ARCHIVES OF PATHOLOGY

VOLUME 14 AUGUST, 1932 NUMBER 2

# CALCIFICATION OF THE MYOCARDIUM IN A PREMATURE INFANT

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Though pathologic calcification is not uncommon, calcific changes in the myocardium are rare. Forty-four cases have been reported, but the records of only forty-one, including the case presented here, could be obtained, and of these many were incomplete. Of these forty-one cases, twenty occurred in males and twelve in females; in the reports of the nine remaining cases, the sex was not given. In twenty-one instances, the ages ranged from 21 to 60 years. The youngest patient was the one whose case is reported in this paper, namely, a 26 weeks premature infant; the oldest was aged 86 years.

The accompanying table shows that calcification of the muscle fibers is secondary to necrosis or to certain forms of degeneration, except fatty degeneration. In only one case (Sturzenegger's [1]) was necrosis not described, but it is possible that with decalcification necrotic muscle fibers would have been seen. The relationship between fatty degeneration and calcification is shown by Robin,[2] Hart,[3] Pappenheimer [4] and Roth [5] to be of no significance. This is in accordance with my findings. Only Stumpf [6] observed some muscle fibers with both fatty degeneration and calcification, and even he concluded that the relationship is unusual.

The causes for the necrotic (degenerative) changes in the muscle fibers were used as a basis for classifying the cases summarized in the table. This table brings out three main groups, namely, the vascular, the inflammatory and the toxic. These will be discussed in detail later, although I may say at this point that there is not a pure case of calcium metastasis involving the cardiac muscle fibers reported in the literature.

The case now reported is interesting because, as mentioned, it occurred in the youngest of all the subjects so far observed, and because it illustrates clearly the pathogenesis of the calcification.

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1. Sturzenegger, E.: Beitr. z. path. anat. u. z. allg. Path. **78**:85, 1927.
2. Robin, A.: Bull. et mém. Soc. méd. d. hôp. de Paris **2**:99, 1885.
3. Hart, C.: Frankfurt. Ztschr. f. Path. **3**:706, 1909.
4. Pappenheimer, A.: Proc. New York Path. Soc. **10**:129, 1910.
5. Roth, M.: Cor.-Bl. f. Schweiz. Aerzte **9**:226, 1884.
6. Stumpf: Centralbl. f. allg. Path. u. path. Anat. **25**:801, 1914.

REPORT OF A CASE

The mother, a 24 year old primipara, white, married, was admitted to the Cook County Hospital on Oct. 7, 1931. She was six and a half months pregnant, in the second stage of labor, and was delivered of a female fetus that died thirty minutes after birth with signs of cardiac failure.

At autopsy, the heart weighed 16 Gm. The epicardium was thin, transparent and smooth. Three fourths of the apex was formed by the left ventricle, the wall of which measured 6 mm., while that of the right ventricle measured 3 mm. The myocardium was light purple-gray with some yellow, and was soft. The left ventricle was slightly dilated, its transverse diameter being equal to its vertical diameter, which was 28 mm. The endocardium of the left ventricle was thin and transparent, but the trabeculae carneae were slightly flattened. None of the valves showed changes. In striking contrast to the thin, smooth and elastic aorta, the first measurement of which was 19 mm., the wall of the right auricle was rigid, owing to the presence of yellowish-white deposits, which to a large extent had

Fig. 1.—Roentgen picture of the fresh heart showing the linear deposits of calcium in the right auricle and irregularly scattered deposits of calcium in the walls of both ventricles.

singled out the trabeculae carneae, making them appear as distinct, yellowish-white, linear bundles. The auricle measured 21 by 15 by 12 mm.; its wall was as much as 3 mm. in thickness, and its endocardium was smooth. The appendage of the right auricle was soft. The foramen ovale was anatomically patent.

The other anatomic findings were: marked intermeningeal hemorrhages, especially in the region of the temporal lobes; marked edema of the brain; edema and hyperemia of the leptomeninges; subaponeurotic and subcutaneous hemorrhages of the scalp; marked edema of the scalp and face; passive congestion of the liver, spleen and kidneys; edema of the lungs; ascites, and prematurity.

In order to determine the extent of the calcification more exactly, an x-ray picture of the fresh heart was taken (fig. 1). Here one plainly sees the marked involvement of the right auricle and irregularly scattered deposits of calcium in the walls of both ventricles.

*Microscopic Observations.*—In the right auricle there were extensive deposits of calcium, which appeared in the form of coarse and branched trabeculae (fig. 2).

In many places, the calcification involved the entire thickness of the wall from the epicardium to the endocardium, which was markedly thickened. The remaining muscle fibers were narrow, particularly those in close proximity to the deposits of calcium, and appeared as slender bands with elongated nuclei. In some places near the fibrous ring of the tricuspid valve, there were interstitial accumulations of small round cells, which were arranged about thin-walled capillaries. The interstitial accumulations were surrounded by fibrillar connective tissue, which extended between the adjacent muscle fibers. Some of the muscle fibers thus became isolated and separated from the other fibers.

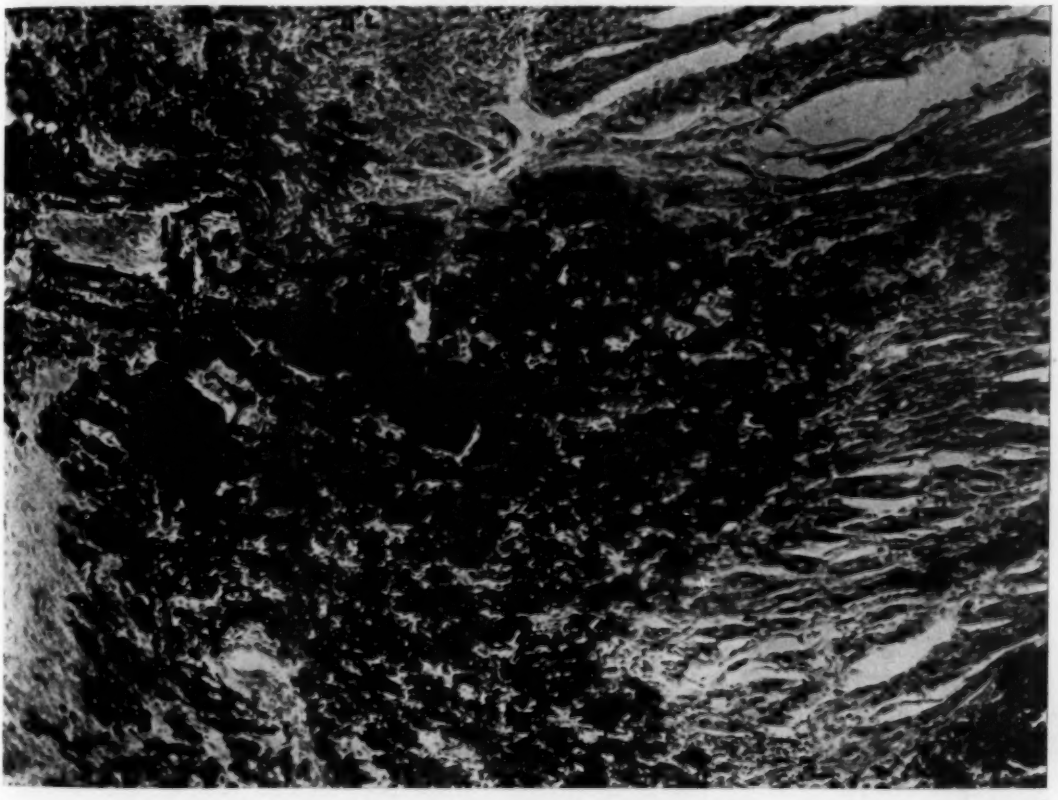

Fig. 2.—Wall of right auricle showing extensive calcification. The origin of the deposits of calcium from the muscle fibers is well shown in the upper left corner of the picture. Formaldehyde fixation; celloidin section; Kossa stain counterstained with alum carmine; reduced from a magnification of × 120.

In the right auricular appendage practically all the muscle fibers had been substituted by calcium, and the derivation of the calcium trabeculae was clearly shown. Not only did the calcium trabeculae imitate the outlines of the muscle fibers, but they also showed their characteristic arrangement. During decalcification of the section with hydrochloric acid, gas bubbles were formed. The decalcified muscle fibers were seen to be without striations, their nuclei were irregular, and the fibers appeared swollen. Fat stain did not show any sudanophil material. The calcified

structures did not show any relation to the elastic fibers, and no iron was found in the sections. Between the calcified muscle fibers there was a moderate amount of loose, fibrillar connective tissue, which in places became densely infiltrated by small round cells.

Scattered throughout the myocardium of the right ventricle were small, irregular areas of increase of the interstitial tissue. Some of these areas were composed of fibrillar connective tissue, while others were rich in small, round cells. The muscle fibers were fairly well preserved.

The changes in the left auricle were similar to those described in the right auricle, although they were less pronounced. There was an occasional isolated muscle fiber which was calcified and surrounded by fibrillar connective tissue, loosely infiltrated by small round cells. There were, however, also places in which larger groups of muscle fibers were completely calcified.

There were many small interstitial accumulations of small round cells in the anterior wall of the left ventricle and an occasional focus of calcification of the muscle fibers, which was much less pronounced than in the auricles. These infiltrations occupied chiefly the central parts of the myocardium.

In the septum, the interstitial infiltrations were scanty, being found especially beneath the endocardium. When present, they were associated with calcification of the muscle fibers.

In the center of the papillary muscle of the left ventricle there was a large deposit of calcium in the form of coarse trabeculae. The deposition was surrounded by connective tissue and loosely scattered small round cells. Some of the muscle fibers near the calcified areas showed an increased affinity to the eosin stain.

The aorta and pulmonary artery did not show any abnormal changes.

The suprarenal cortex was well developed, and in particular the glomerular zone was prominent. In the reticularis, near the medulla, there were small round or cuboidal calcium deposits that reached the size of a cortical cell. In some places, the cortical cells accumulated and formed small pleomorphic nodules (cortical adenomas).

## COMMENT

It is evident that the calcification of the myocardium in this case was secondary to degenerative changes in the muscle fibers. Areas of calcification of the interstitial tissue as described by Robin,[2] Roth,[5] Askanazy,[7] Scholz,[8] Hedinger (case 2[9]), Geipel[10] and Siebenmann[11] were not found. There were some groups of muscle fibers showing hyaline degeneration that were surrounded by normal myocardium or were adjacent to calcified muscle fibers. In other places fibrous tissue was seen surrounding them. Further, areas of calcification might be seen surrounded either by normal muscle fibers or by scar tissue. There were also areas of muscle fibers separated from each other by scar tissue, but this finding is explained by the fact that the section was cut tangentially through the interstitial proliferated stroma surrounding areas of calcification. In some places there were accumu-

7. Askanazy: Festschr. z. Feier d. 60 Geburtst. v. M. Jaffe, 1901, p. 187.
8. Scholz, T.: Arch. Int. Med. **34**:32, 1924.
9. Hedinger: Verhandl. d. deutsch. path. Gesellsch. **11**:295, 1907-1908.
10. Geipel, P.: Fortschr. a. d. Geb. d. Röntgenstrahlen Hamb. **34**:311, 1926.
11. Siebenmann, F.: Inaugural Dissertation, Basel, 1909.

lations of round cells, but polymorphonuclear leukocytes were not found. The former were found in relation to the calcified masses. The sections stained with sudan III showed clearly that fatty degeneration played no rôle in the calcification of the muscle fibers. In brief, one could distinguish three distinct processes: hyaline degeneration of the muscle fibers, deposition of calcium and reactive proliferation of the stroma. These changes could be correlated as follows: The degeneration of the muscle fibers was apparently primary and was followed by calcification. The calcium acted as a foreign body and caused a reactive proliferation of the stroma. This conception is also held by Wiechert,[12] Pappenheimer,[4] Hart,[3] Fischer [13] and others.

The question now arises as to the cause of the degeneration. The degeneration could not have been due to vascular changes, since macroscopically and microscopically the aorta and coronary arteries were thin-walled, and the coronary arteries everywhere were patent. An infectious origin also could be ruled out, because there were no signs of inflammation in the heart save those secondary to the calcification. It was not a case of calcium metastasis (Virchow [14]); for the skeleton showed no abnormalities on roentgen examination, the muscle fibers that were calcified were degenerated, and finally the calcium deposits had no relationship to the coronary arteries. Thus it is most likely that the cause of the degeneration was toxic. There were no evidences of infection in the child; therefore one has to assume that the toxic agent might have come from the mother. I attempted to obtain information concerning the presence of some infection or intoxication during the pregnancy, but unfortunately I was unable to do so because the mother had left the hospital and could not be located.

There are three cases reported in the literature that resemble the one now reported in the matter of age: Jacobsthal's,[15] which differs because definite inflammation was present in the anterior papillary muscle; Fischer's,[13] different in that both endocarditis and myocarditis were present, and Sturzenegger's,[1] different because the infant had fetal meconium peritonitis as the cause for the degeneration of the myocardium.

Other cases of toxic necrosis of the myocardium have been reported by Coats,[16] Wiechert,[12] Pappenheimer,[4] Tilp [17] and Liebscher,[18] but in these the patients were from 26 to 48 years of age. In this connection it may be mentioned that Iff [19] recently reported a case of a new-born

12. Wiechert, A.: Inaugural Dissertation, Marburg, 1907.
13. Fischer, B.: Frankfurt. Ztschr. f. Path. **7**:83, 1911.
14. Virchow: Virchows Arch. f. path. Anat. **8**:108, 1855; **9**:618, 1855.
15. Jacobsthal: Virchows Arch. f. path. Anat. **159**:361, 1900.
16. Coats: Glasgow M. J. **4**:433, 1872.
17. Tilp: Verhandl. d. deutsch. path. Gesellsch. **15**:471, 1912.
18. Liebscher, C.: Prag. med. Wchnschr. **27**:181, 1902.
19. Iff, W.: Virchows Arch. f. path. Anat. **281**:377, 1931.

child in whom the media and to a lesser extent the intima and adventitia of the large and medium-sized arteries were calcified. He similarly explained the changes on the basis of toxic necrosis of the media with secondary calcification.

### REVIEW AND CLASSIFICATION OF CASES IN THE LITERATURE

From the table it can be seen that the causes of degeneration of the muscle fibers fall into three groups. The first of these is the vascular,

*Etiology of Primary Degeneration in Calcification of the Myocardium*

I. Vascular Group (coronary Occlusion)
- A. Coronary sclerosis
  - 1. Burns
  - 2. Robin
  - 3. Askanazy
  - 4. Scholz
- B. Coronary thrombosis
  - 1. Stumpf
  - 2. Davidson
- C. With granular kidney
  - 1. Heschel
  - 2. Hedinger (case 2)
  - 3. Geipel
  - 4. King

II. Inflammatory Group
- A. Pyogenic abscess
  - 1. Hardrichs
- B. Tubercle
  - 1. Püschman
- C. Myocarditis
  - 1. Jacobsthal (etiology?)
  - 2. Hart (chronic syphilis)
- D. Myocarditis and endocarditis (rheumatic)
  - 1. Fischer
  - 2. Krayn
- E. Pancarditis (rheumatic)
  - 1. Cutler and Sosman (case 1)
- F. With pericarditis
  - 1. Bordenave (cause?)
  - 2. Simmons and Watson (pneumococcic)
  - 3. Burnet (pneumococcic)
  - 4. Drummond (pneumococcic)
  - 5. Cutler and Sosman (case 2 pneumococcic)

III. Toxic Group
- A. Infectious toxemia (chronic sepsis)
  - 1. Chronic bronchitis (Coats, case 1)
  - 2. Relapsing fever with pyemia (Coats, case 2)
  - 3. Chronic tuberculosis (Liebscher)
  - 4. Infection with B. paratyphosus (Wiechert)
  - 5. Gangrenous appendicitis with suppurative peritonitis, hepatic abscess, etc. (Pappenheimer)
  - 6. Chronic bronchiectasis empyema (Tilp)
- B. With destruction of bone
  - 1. Chronic osteomyelitis of hand (Roth)
  - 2. Chronic osteomyelitis of long bones (Siebenmann)
- C. Noninfectious toxemia
  - 1. Chronic lead poisoning (Langerhanz)
  - 2. Eclampsia (Roessle
  - 3. Meconium peritonitis (Sturzenegger)
  - 4. Bichloride of mercury poisoning (Reuther)

IV. Unclassified Group
1. Rokitansky
2. Topham
3. Hedinger (case 1) (toxic—cause?)
4. Diamond (toxic—cause?)

V. Group, the Records of Which Were Unobtainable
1. Allen
2. Benjaminovich (2 cases)
3. Waldorp

and in it are included all those cases in which the degeneration followed coronary occlusion whether due to sclerosis, thrombosis or spasm. In four cases, coronary sclerosis was the important factor.

Burns [20] reported the case of a man with advanced arteriosclerosis, thrombosis of the left auricle, marked coronary sclerosis and irregular calcified areas in the left ventricle. Robin [2] reported the case of an 85 year old man who died from right hemiplegia, and who at autopsy showed sclerotic aorta and coronary arteries, a calcareous plaque in the

20. Burns, A.: Some of the Most Frequent and Important Diseases of the Heart, Edinburgh, Bryce & Company, 1809, p. 340.

endocardium of the left side of the interventricular septum and, microscopically, in the left ventricle, in areas of fibrous tissue, around partially obstructed arterioles, "fine strands which gave gas when treated with hydrochloric acid." Askanazy [7] wrote on a case of a woman 36 years old with coronary sclerosis and irregular areas of calcification in the wall of the left ventricle. Finally, Scholz [8] reported a case of massive calcification of the left ventricle especially at the apex in a man 74 years old, whose left coronary artery was almost occluded by calcific plaques.

The cases of Stumpf [6] and Davidson [21] illustrate coronary thrombosis as the cause of the necrosis.

Four cases are associated with granular contracted kidneys, and since myocardial degenerations in these cases are often due either to arteriolosclerosis or to coronary spasms, they have been included in the vascular group. The first was that observed by Heschl [22] in 1861; the patient had classic Bright's disease and showed at autopsy contracted kidneys. Calcium carbonate was found in broken up heart muscle fibers. He was incorrect in believing this to be a case of calcium metastasis in spite of the absence of destruction of bone. The second, Hedinger's [9] second patient, had contracted kidneys and calcified masses in the left and right ventricles. The third case (Geipel [10]) concerned a 15 year old girl who died in uremia and showed calcification of the right auricle, septum and anterior papillary muscle. The coronary arteries were slightly involved also. The last, described by King,[23] was the case of one who died in uremia and in whom microscopically irregular areas of calcification were found.

In the second group of cases true inflammatory conditions were present, including: a myocardial abscess with calcified wall (Hardrichs [24]), a calcified tubercle in the myocardium (Püschman [25]) and focal myocarditis with calcium in the degenerated muscle fibers (Jacobsthal [15]). In Hart's [3] case there was congenital syphilis and recent verrucous endocarditis, and microscopically there were numerous areas of focal inflammation with infiltration by leukocytes as well as by monocytes. Calcium was found in destroyed muscle fibers. Hart believed that amyloid, hyaline and glycogenic degenerations may be the basis for calcium depositions. The finding of hyaline degeneration in my case supports this theory, and, indeed, Beneke and Bönning [26] showed a relationship between amyloid and calcification. Fischer's [13] case was one of fetal

21. Davidson, T. W.: Brit. M. J. **1**:212, 1928.
22. Heschl: Oesterr. Ztschr. f. prakt. Heilk. **7**:49, 1861.
23. King, V. de P.: Ann. Int. Med. **2**:936, 1929.
24. Hardrichs: M. Rec. **18**:552, 1880.
25. Püschman: Inaugural Dissertation, Leipzig, 1896; abstr., Centralbl. f. allg. Path. u. path. Anat., 1897.
26. Beneke and Bönning: Beitr. z. path. Anat. u. z. allg. Path. **44**:362, 1908.

endocarditis and myocarditis, and microscopically many varieties of cells including leukocytes were found in the myocardium as was calcium in the degenerated muscle fibers. In Krayn's [27] case there was a double mitral lesion due to old rheumatic endocarditis probably associated with myocarditis, and calcium was found deposited in broken up muscle fibers. Cutler and Sosman [28] reported a case (1) of a 26 year old woman with recurrent attacks of rheumatic fever and who at autopsy gave evidence of pancarditis with calcification of the papillary muscles, pulmonary and mitral leaflets and pericardium.

In each of the next six cases listed in the table (Bordenave,[29] Simmons and Watson,[30] Burnet,[31] Drummond,[32] Lucas [33] and Cutler and Sosman [28] [case 2]) there was found calcification of the pericardium with the calcification extending into the ventricles, being due to myocarditis associated with the pericarditis or to toxic degeneration of the myocardium due to the pericarditis.

The third group consists of cases of toxic necrosis, infectious or noninfectious, of the muscle fibers. The infectious subgroup includes cases of chronic bronchitis (Coats [16] [case 1)]; relapsing fever with pyemia and abscesses in the lungs, parotid glands, kidneys, etc. (Coats [16] [case 2]); sepsis due to paratyphoid B infection (Wiechert [12]); gangrenous appendicitis with suppurative peritonitis, suppurative thrombophlebitis, etc. (Pappenheimer [4]); chronic bronchiectasis with pleural empyema (Tilp [17]), and chronic pulmonary and glandular tuberculosis (Liebscher [18]).

In the next two cases, the etiologic factors are chronic infectious toxemias with destruction of bone, and therefore these resemble calcium metastasis. The first (Roth [5]) concerns a 29 year old man who had chronic osteomyelitis of the hand with septicemia, calcium being found in the degenerated muscle fibers in the ventricles and auricles of the heart, in the glomeruli and tubuli of the kidneys and in the interstitial tissue of the mucosa of the stomach. Roth considered the condition to be one of calcium metastasis and probably was correct in the case of the kidneys and the stomach, but the fact that the degenerated muscle fibers were calcified and that the calcium deposits did not have the typical relationship to the blood vessels makes the possibility of a toxic degeneration due to the chronic osteomyelitis more acceptable. The second case described by Siebenmann [11] concerned a 36 year old man

27. Krayn, M.: Inaugural Dissertation, Heidelberg, 1914.
28. Cutler, E. C., and Sosman, M. C.: Am. J. Roentgenol. **12**:312, 1924.
29. Bordenave, M.: Mém. Acad. roy. d. sc., Paris, 1768.
30. Simmons, S. F., and Watson, H.: London Medical Communications, 1783, p. 228.
31. Burnet, R. W.: Tr. Path. Soc., London **32**:53, 1881.
32. Drummond, D.: Am. J. M. Sc. **99**:153, 1890.
33. Lucas, J. J. S.: Brit. M. J. **2**:1404, 1907.

with chronic advanced osteomyelitis and cystic degeneration of the long bones and chronic nephritis. Extensive calcification was found in the degenerated heart muscle fibers and also in the interstitial tissue, being most abundant about the blood vessels. The lungs, kidneys and liver also showed calcium. This case, again, probably should not be considered one of true calcium metastasis, because the degenerated heart muscle fibers were calcified. A toxic degeneration is more probable.

Included under noninfectious toxemias resulting in calcification of the myocardium are chronic lead poisoning (Langerhanz [34]), eclampsia (Roessle [35]), fetal meconium peritonitis (Sturzenegger [case 1]) and bichloride of mercury poisoning (Rüther [36]). The possibility of degeneration of the myocardium due to bichloride of mercury must be kept in mind in Tilp's [17] case, even though the patient died about two and a half days after he had taken the drug.

The records of Rokitansky's,[37] Topham's [38] and the first of Hedinger's [9] cases are so incomplete that they cannot be classified. Though the hyaline degeneration of the muscle fibers in the case in this paper is assumed to have been due to a toxic factor, the cause could not be ascertained.

Finally, Morgagni [39] and von Recklinghausen [40] merely mentioned that they had seen cases of calcification of the myocardium, while the reports of Allen,[41] Benjaminovich [42] and Waldorp [43] were unobtainable, and Oppenheimer's [44] case showed only endocardial changes.

SUMMARY

In a 26 weeks old, premature infant who lived for thirty minutes after birth, extensive calcification of the myocardium was found, which is explained as secondary to toxic degeneration of the muscle fibers. A review of the literature shows that calcification of the myocardium is secondary to preceding degeneration or necrosis of the muscle fibers. This degeneration may be due to vascular, inflammatory or toxic conditions. Fatty degeneration plays no part in calcification of the muscle fibers.

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34. Langerhanz: Grundriss der allgemeinen Pathologie und pathologischen Anatomie, Berlin, 1902, p. 419.
35. Roessle: Verhandl. d. deutsch. path. Gesellsch. **10**:303, 1907-1908.
36. Rüther, A.: Ztschr. f. Kreislaufforsch. **21**:313, 1929.
37. Rokitansky, C.: Ztschr. d. k. k. Gesellsch. d. Aertz in Wien **1**:1, 1849.
38. Topham: Brit. M. J. **2**:953, 1906.
39. Morgagni: De sedibus et causis morborum, Venetiis, ex typog. Remondiniana 1762, epist. 27, art. 16.
40. von Recklinghausen: Handbuch der allgemeinen Pathologie des Kreislaufes und der Ernährung, Stuttgart, Ferdinand Enke, 1883.
41. Allen: Australian M. J. **6**:69, 1884.
42. Benjaminovich: Sibirsk.-Vrach. **2**:139, 1915.
43. Waldorp, C. P.: Rev. Asoc. méd. argent. **37**:74, 1924.
44. Oppenheimer, B. S.: Proc. New York Path. Soc. **12**:213, 1912.

# ACUTE PYEMIC CHOLECYSTITIS

## REPORT OF A CASE

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Pronounced hematogenous infection of the gallbladder in pyemia is exceptionally rare. Not one such occurrence was noted in 12,000 postmortem examinations at the German Pathological Institute, Prague, during the past twelve years, despite the fact that among these necropsies were many cases of pyemia. Kaufmann [1] reported briefly two examples of septicopyemia in which at autopsy a fair number of pustules were found in the mucosa of the gallbladder. These changes possessed no clinical significance. Except for Kaufmann's observations, the literature, so far as we have been able to determine, reveals no similar instances, completely described.

A recent case of advanced acute cholecystitis with many embolic lesions without stones, in an anatomically typical staphylococcic pyemia arising from acute osteomyelitis, seems worthy of a report. Of significance are its extreme rarity, its unusual gross and microscopic appearances and its clinical importance.

### REPORT OF CASE

*Clinical History.*—A married white woman, aged 58, was admitted to the Buffalo General Hospital, in the service of Dr. Nelson G. Russell, Sept. 17, 1931, because of pain in the right hypochondrium and back. She died the next day. The family history was unimportant. Four years before her entry into the hospital, she had suffered from a condition which was diagnosed as diabetes mellitus.

The illness in question began a little over a week before admission with a moderately severe pain in the lower part of the back and a slight fever. Minimizing her complaints to the family physician who saw her at this time, she continued up and about, working. Two days later, however, she was forced to bed with a severe pain in the right hypochondrium and fever. Nausea and emesis occurred several times. Acute cholecystitis now suggested itself to her physician. Subsequently her condition became more serious; the abdominal pain was not

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1. Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte, ed. 9-10, Berlin, W. de Gruyter & Co., 1931, vol. 1, p. 929.

relieved, while the pain in the back radiated downward to the thighs and increased to such a degree that she was unable to lie flat in bed; finally semicoma supervened.

The temperature was 99 F.; the pulse rate, 90, and the respirations, 26. The blood pressure was 110 systolic and 72 diastolic. The skin showed no jaundice. Many râles were heard at the bases of both lungs. "Exquisite tenderness" was elicited in the region of the gallbladder. The right upper quadrant was held tense, but not rigid.

The laboratory studies showed diabetes mellitus of moderate severity without significant acidosis, and polymorphonuclear leukocytosis. A blood culture gave six colonies of Staphylococcus aureus per cubic centimeter.

*Anatomic Diagnosis.*—The autopsy was made one hour after death. The anatomic diagnosis was: acute, purulent osteomyelitis and periostitis of the body of the third and fourth lumbar vertebrae, extending on the right side into the iliopsoas muscle, with purulent myositis; acute lymphadenitis of the peri-aortic nodes;

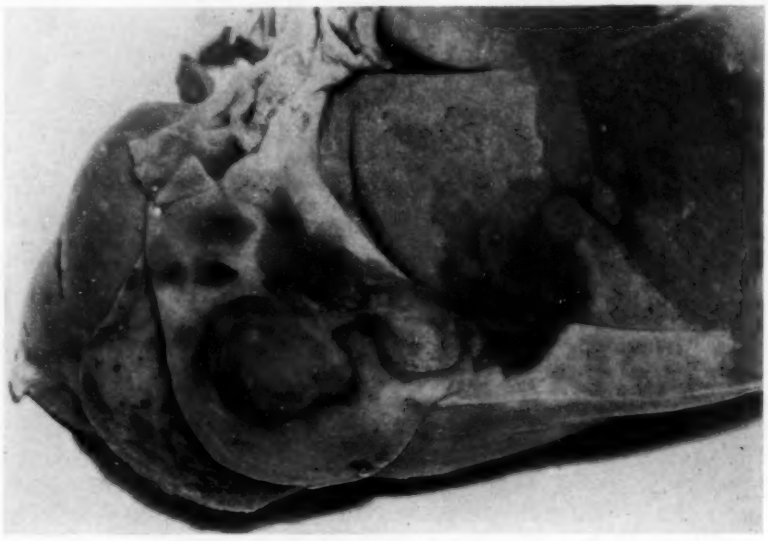

Fig. 1.—External view of gallbladder.

staphylococcic pyemia; multiple pyemic lesions of embolic nature in the wall of the gallbladder, with erosions and ulcers of the mucous membrane, and extension outward to the serosa with the formation of acute purulent pericholecystitis and right subdiaphragmatic abscess; pyemic, hemorrhagic infarcts in both lungs, with fibrinous pleuritis; multiple pyemic abscesses of both kidneys; slightly enlarged, somewhat soft spleen; diffuse colloid hyperplasia of the thyroid.

*Gallbladder.*—When the peritoneal cavity was opened, about 200 cc. of bile-stained, purulent, odorless material escaped from the area beneath the costal arch on the right side. The gallbladder seemed somewhat distended and was bound to the colon by recently formed fibrinous shreds. Its shape and position were entirely normal. On the external free surface (fig. 1) appeared a large, flat, pouchlike protrusion of the wall, like a dumb-bell in shape, green, and covered with a thin, fibrinopurulent exudate. Near the neck of the gallbladder were three other yellowish-green patches, from 0.4 to 0.7 cm. in diameter. In addition, the external

free surface was marked with several smaller round, greenish patches, apparently extensions from focal lesions in the wall.

On incision, a fair amount of greenish, mucoid bile escaped. The open gallbladder showed an interesting picture (fig. 2). No stones were present. The mucosa was spotted with rather numerous ulcers and erosions of various sizes with chrome yellow centers, corresponding to the patches noted externally, the circumferences being stained distinctly green from bile imbibition. Two ulcers on the internal free surface, one measuring 2 by 1 cm., the other 1.4 by 1.6 cm., almost ran together, in the dumb-bell-shaped manner indicated. A few pea-sized erosions were noted on the internal free surface throughout the region of the neck. Similar medium-sized erosions were scattered on the internal upper surface. Between these large and medium-sized ulcers and erosions were sprinkled small erosions of about pencil-point size and dark green. The mucosa otherwise showed

Fig. 2.—Internal view of gallbladder.

distinct injection. No real abscesses and no small pustules were present. The wall showed no appreciable thickening; in its thickest portion it measured 0.2 cm. The intrahepatic, hepatic, cystic and common bile ducts were not dilated. Their mucosa was not injected, and the bile which they contained was normal in appearance. The cystic duct node was completely surrounded by fat and apparently not swollen. The portal vein and hepatic arteries were normal. The pus that exuded when the abdomen was first opened came from a large abscess bounded by the diaphragm, parietal wall, liver, colon and right kidney, the upper pole of which was 5 cm. lower than that of the kidney of the other side. The liver was slightly atrophic and rather soft. In many cross-sections no abscesses were observed.

The pancreas weighed 25 Gm.

*Bacteriology.*—Smears from the bone and periosteum of the third and fourth lumbar vertebrae, iliopsoas muscle, subdiaphragmatic abscess, kidneys, wall of the gallbladder, bile in the gallbladder and hepatic and cystic ducts revealed an unusually large number of staphylococci. No other micro-organisms were seen.

*Microscopic Examination.*—Sections of the gallbladder were made from different parts, including the large deep ulcers, superficial erosions, neck and uninvolved areas. The cystic duct was also examined. Hematoxylin-eosin and Gram-Weigert bacterial stains were used. The histologic picture of the different embolic lesions, erosions and ulcers, noted grossly, was clear and similar in all the sections examined, but rather unusual. Throughout, it was characterized primarily and uniformly by the presence within capillary vessels, as well as in the wall of the gallbladder adjacent to them, of large bacterial masses with marked necrosis and extensive recent hemorrhage of the surrounding tissue. The changes in the necrotic tissue resembled definite autolysis, which was confined to the vicinity of the bacterial masses. The different histologic lesions tended to be trapezoid or wedge-shaped. Forming the borders of a few necrotic foci many leukocytes were observed, but principally near a majority of the embolic necroses there was almost complete absence of severe reactive cellular infiltration. Rather surprising was this unusual general lack of distinct abscess formation. In the wall forming the margin of bacterial masses that could be traced in the deep layers—for instance, in the bases of small ulcers and recent erosions—we found only a moderate number of lympho-

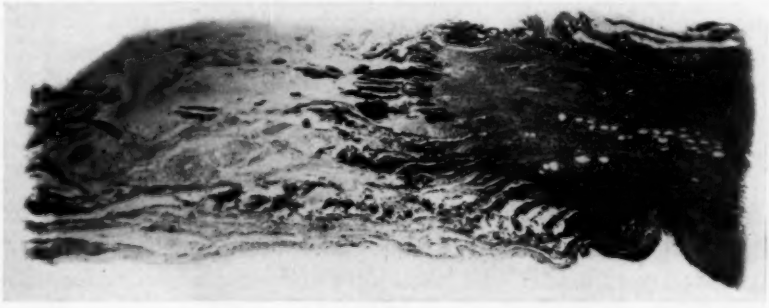

Fig. 3.—Huge focus with marked necrosis involving all layers of the wall extending to the serosa, and with large bacterial masses on its margin. The mucosa is destroyed. The wall adjacent to the focus is relatively unaffected; the mucosa here is still preserved, and the cellular reaction is minimal; low power magnification.

cytes and a distinct proliferation of young mesenchymal cells, the remainder of the adjacent wall not being remarkable. At the bases of large ulcers, a few leukocytes with inflammatory edema were occasionally seen. In some sections, especially in the large subserous abscess-like foci, the serosa, which was in most parts only distended and free from surface exudate, showed, along with the marked inflammatory edema, a rather pronounced leukocytic, almost phlegmonous inflammation and fibrinous exudation. Much of the mucosa on the surfaces of recent superficial lesions was preserved, overhanging, almost covering the whole area of each embolic focus; the mucosa opposite the inner surfaces of deep foci was usually entirely normal.

Examination of those parts of the gallbladder in which grossly no erosions or embolic foci were seen, and of the cystic duct, showed only injection of the veins and slight edema of the subserous tissue. Especially noteworthy was the absence of any fibrosis or signs of rebuilding of the wall, such as are found in chronic cholecystitis. The mucosa was not changed.

In many sections of the liver no abscess formations were seen.

The right iliopsoas muscle showed dissecting interstitial, almost phlegmonous inflammation with very large abscess formation and necrosis of the muscle fibers.

In the peri-aortic nodes was found inflammatory hyperplasia with leukocytic exudate into the sinuses with marked swelling of the reticulum cells.

The kidneys disclosed typical excretory abscesses in an early stage with bacterial masses in the centers.

In the tail and body of the pancreas the islands of Langerhans were decreased in number.

The lungs showed septic hemorrhagic infarctions in rather early stages.

## COMMENT

This case seems explained satisfactorily by the occurrence of primary acute osteomyelitis of the lumbar vertebrae and staphylococcic pyemia, followed soon after by acute pyemic cholecystitis, which completely dominated the clinical picture.

The anatomic and histologic findings make it clear that in the wall of the gallbladder were multiple severe pyemic lesions of embolic nature, characterized by the presence of large bacterial masses and severe necrosis, but by the absence of abscess formation, extending to the serosa, and thence causing, without a distinct gross perforation, acute focal peritonitis.

The lesions in the wall of the gallbladder can be accounted for only on a hematogenous basis. The condition was one of typical pyemia with a positive blood culture of S. aureus. The histologic changes began in the deeper layers of the wall, the ulcers and erosions occurring secondarily. They consisted fundamentally of multiple bacterial emboli in capillary vessels with invasion of the surrounding tissue by bacteria, and with involvement of the invaded tissue by necrosis and extensive hemorrhage.

The presence of bacteria in the bile can almost certainly be explained by direct passage of micro-organisms into the lumen from perforating lesions in the deeper layers of the wall of the gallbladder, rather than by excretion of those organisms with the bile from the liver into the ducts, with subsequent descending infection of the gallbladder. In many sections of the liver, no abscesses or areas of necrosis were found. There were no stones or occlusions of the cystic or common bile ducts, and in the absence of such factors it has proved until now impossible, by experimental introduction of virulent bacteria into the gallbladder, to produce cholecystitis. The erosions in different areas of the gallbladder resembled in no way decubitus ulcers caused by stones. It is perhaps interesting to note here that the bile in two other cases of pyemia in which autopsies were made recently, one due to acute staphylococcic osteomyelitis of the left femur and the other to strep-

tococcic infection of the upper respiratory tract, proved to be sterile on culture. That the gallbladder had been the seat of previous recurrent inflammatory attacks is improbable, because no thickening of the wall, no fibrosis of the subserosa and no scar formation in the mucosa were demonstrable.

An analysis of the histologic picture leads to the conclusion that the changes produced by the unusually large bacterial emboli must be considered as infarcts or anemic necroses, rather than as real abscesses. The marked necrosis with severe hemorrhage around the bacterial masses, and in a few instances with an additional outer border of marked leukocytic infiltration, together usually forming a wedge-shaped focus, supports from a structural point of view the conception of a process of acute embolic necrosis or infarction. No real abscesses or pustules, such as Kaufmann described, were seen in this case. Yet the lesions in the gallbladder, in view of the clinical history, could hardly have been antedated by those in the kidneys, which were typical pyemic abscesses. We can only speculate whether some lesions had already extruded their purulent content into the lumen of the gallbladder by perforation through the mucous membrane, or whether leukocytic infiltration had no favorable opportunity to appear in the face of an overwhelming infection progressing rapidly with marked necrosis through the loose tissue in the thin-walled organ.

The localized peritonitis and subdiaphragmatic abscess, in the absence of a demonstrable gross perforation, probably occurred by penetration of organisms at the site of the dumb-bell-shaped serosal protrusion. We believe that at these points there was rapid penetration through large sections of excessive necrosis within the wall.

## SUMMARY

The clinical record and pathologic findings in an unusual case of advanced acute pyemic cholecystitis with multiple embolic lesions in the wall of the gallbladder, which occurred during staphylococcic pyemia arising from acute osteomyelitis of the lumbar vertebrae, are reported. No similar observation appears in the literature. Grossly, the internal surface of the gallbladder showed superficial erosions and ulcers; externally, without a gross perforation, the formation of acute pericholecystitis and right subdiaphragmatic abscess had taken place. No real abscesses were found in the wall of the gallbladder. Histologically, the lesions observed in the wall were best characterized as acute infarctions from bacterial emboli. Clinically, the symptoms referable to the pathologic changes in the gallbladder tended to obscure all other manifestations of the primary disease with which the patient, an elderly diabetic woman, was suffering.

# VASCULAR LESIONS OF THE GASTRO-INTESTINAL TRACT IN MERCURY POISONING

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On Dec. 11, 1927, a patient who had suffered for nine days with acute abdominal pain, associated with chills, fever and night sweats, was examined post mortem. The examination revealed 25 cm. of gangrenous ileum which had become completely separated from the canal by sharp lines of demarcation. The mesentery leading to this segment of intestine was markedly thickened and indurated. The rest of the gastro-intestinal tract was normal. It was obvious that there was marked vascular injury in this part of the mesentery. The cause of the injury was not apparent at the time, but we are inclined, as a result of subsequent studies, to ascribe it to the ingestion of mercuric chloride administered in the course of antisyphilitic treatment.

On Nov. 26, 1929, another patient who had been ill with diarrhea for two years, and who recently had exhibited evidence of peritonitis, was examined post mortem. The examination established that the terminal 3 feet (92 cm.) of ileum was ulcerated, and that the mesentery was much thickened. There were perforations at the ileomesenteric angle. This, again, indicated nutritional disturbance of a limited portion of the intestinal wall. According to the patient's history, a persistent diarrhea followed immediately on the taking of thirty doses of mild mercuric chloride at intervals of thirty minutes. The pathologic changes suggested the case noted in the preceding paragraph. As it was realized that mercury might cause the extensive vascular lesions of the order found, 517 Gm. of involved mesentery and intestine was chemically analyzed for mercury, and 3.88 mg. of metallic mercury was recovered.

In a third instance, in the fall of 1931, the ulcerated stomach and thickened, constricted large bowel at postmortem examination were sent to the department for histologic examination. Lesions were revealed which were similar, but more active, than those in our second case in

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which mercury had been found. Mercury poisoning was suspected, and an examination for mercury was made; 317 Gm. of this tissue yielded 12.1 mg. of mercury.

According to present knowledge, the amounts of mercury found in these tissues are distinctly abnormal, since only on occasions are traces of mercury found in the tissues of patients who have amalgam fillings (Schreiber in personal communication). We believe that mercury could have caused the vascular lesions noted. In view of the similarity of the lesions in these three cases and the finding of significant quantities of mercury in the tissues in the two cases in which chemical examinations for mercury were made, the concurrence would seem to indicate a highly probable relationship.

## REPORT OF CASES

CASE 1.—A white switchman, aged 44, who entered the University Hospital on July 6, 1927, had a draining perirectal fistula for four years, dizzy spells for three years and nervousness for two years. His past diseases included, besides the ordinary diseases of childhood, scarlet fever at 3, malaria at 14, pneumonia at 32 and 37, diphtheria at 41, gonorrhea four times and a primary penile lesion at 22 years of age. His recovery from these diseases was apparently uneventful, except for an occasional attack of painless jaundice following the malaria. At the age of 38, he had an attack during which he complained of gas in the stomach and an ache in the abdomen. This was accompanied by jaundice and clay-colored stools. He was treated at a "resort" for six weeks, where considerable mild mercuric chloride was administered (the exact amount could not be ascertained). That same year he suffered with diarrhea for five weeks, during which he noted blood and yellowish mucus in his stools. Four years prior to admission, he had an ischiorectal abscess, which was drained. A persistent draining fistula remained. His dizzy spells were not serious.

Physical examination showed nothing abnormal other than the ischiorectal fistula and slightly thickened peripheral arteries. The Wassermann reaction of the blood was positive; otherwise there were no laboratory findings of significance.

After the administration of six 0.9 Gm. doses of neoarsphenamine, an excision of the perirectal fistulous tract was performed. The recovery was uneventful. He was discharged on Aug. 18, 1927, and during the months of October and November he received two doses of one thirty-second grain (0.002 Gm.) of mercuric chloride by mouth every other day. He returned to the hospital on Dec. 2, 1927, complaining of severe pain in the lower left abdominal quadrant and of nocturnal sweats and chills. This illness began on November 20, with severe cramping pain in the left side of the abdomen. Physical examination revealed an exquisitely tender mass in the left lower quadrant of the abdomen. The urine contained a slight trace of albumin, but no blood. Perforated carcinoma of the sigmoid was diagnosed at operation on Dec. 6, 1927. Blood was passed in the stools following operation. Death occurred five days later, twenty-one days after the symptoms began.

*Autopsy.*—Postmortem examination revealed a well nourished, markedly jaundiced man with no evidence of edema. Investigation of the abdominal contents revealed a large cavity beneath the operative incision, the walls of which were formed by the great omentum, the anterior parietes and a loop of small intestine.

These were agglutinated one to another by fibrinous adhesions. The cavity contained a dirty, fluid material. The loop of intestine involved in the cavity was found to be 25 cm. of the lower ileum. This segment of intestine was completely gangrenous. Its proximal and distal portions had become completely separated by rather sharp lines of demarcation from the canal, so that the lumina of both ends communicated freely with the cavity. The mesentery leading to this segment of intestine was markedly thickened and indurated. The entire intestinal canal below this point contained blood. The remaining gross findings were those of profound sepsis. No neoplasm was found.

*Histologic Observations.*—Microscopic examination of the mesentery leading to the gangrenous segment of bowel revealed very marked obliterative arteritis, involving the majority of the medium-sized vessels. Some of the vessels were occluded by organized thrombi, while others showed marked subintimal connective tissue proliferation resulting in slitlike lumina. Some of the latter vessels were occluded by fibrinous thrombi. The lumina of many small vessels contained fibrinous and hyaline thrombi. Subintimal connective tissue proliferation was present in several of the large vessels, but no occlusion was demonstrated. The supporting fat tissue was markedly and diffusely infiltrated with acute inflammatory cells. A thick layer of fibrin was deposited on the peritoneal surfaces. The liver presented the picture of early diffuse toxic necrosis. The kidneys showed no evidence of acute nephritis. The histologic findings in the remaining organs were those of profound sepsis. A streptococcus was cultured from the mesenteric lymph nodes.

Case 2.—A white plasterer, aged 65, entered the University Hospital on July 9, 1929, complaining of diarrhea, soreness in the right side of the chest and a hacking cough. In July, 1928, he took thirty consecutive doses of mild mercuric chloride at intervals of thirty minutes for an attack of "influenza." A persistent diarrhea of from six to twenty stools a day followed. He had never noticed mucus, pus or blood in his stools. His diet was apparently sufficient prior to his illness. In May, 1929, pigmentation, dryness and scaling of the hands appeared, and at this time a dry cough developed, accompanied by pain in the right side of the chest. His loss in weight was 46 pounds (20.8 Kg.). He stated that his father, mother and maternal grandparents died of diarrhea, but that none of them had dementia or dermatitis.

Physical examination revealed an irritable, emaciated man, whose skin was dry and scaly. Other positive findings were unequal pupils, which reacted 50 per cent to light, tortuous and hardened peripheral arteries, some rigidity of both recti muscles and slight tenderness in the right lower abdominal quadrant. Laboratory examinations revealed an absence of free hydrochloric acid in the stomach and the presence of occult blood and undigested food in the stools. The Wassermann reaction of the blood was negative. The patient was discharged on Aug. 10, 1929, with a tentative diagnosis of pellagra. Because his condition did not improve, he was readmitted on Sept. 14, 1929. Reexamination revealed secondary anemia, an increase in the loss of weight to 78 pounds (35.4 Kg.) and roentgen evidence of mucous colitis. He was discharged unimproved on Oct. 5, 1929. On Nov. 16, 1929, he was again admitted because his symptoms had gradually become more pronounced. The physical findings suggested an acute abdominal condition, which was thought to be peritonitis due to a perforated carcinomatous ulcer of the colon. Death occurred on Nov. 25, 1929, sixteen months after the ingestion of mercury.

*Autopsy.*—Postmortem examination revealed an emaciated man, whose skin over the knees, extensor surfaces of the arms, forearms and back was rippled, scaly and purplish. Brownish pigmentation of the skin was limited to the back of the hands. The peritoneal cavity contained 250 cc. of pus and intestinal content.

Fibrin covered the peritoneum. The cecum, the distal loops of the ileum and the sigmoid colon were densely adherent to each other by fibrous adhesions. Several pockets of pus were discovered between the loops of intestine. After the intestinal canal was thoroughly exposed, it became obvious that the important lesion was in the terminal 3 feet (92 cm.) of the ileum. Marked ulceration of the mucosa of this portion was observed. The ulcerated areas increased in number and size from above downward, until practically the entire mucosa was involved at the

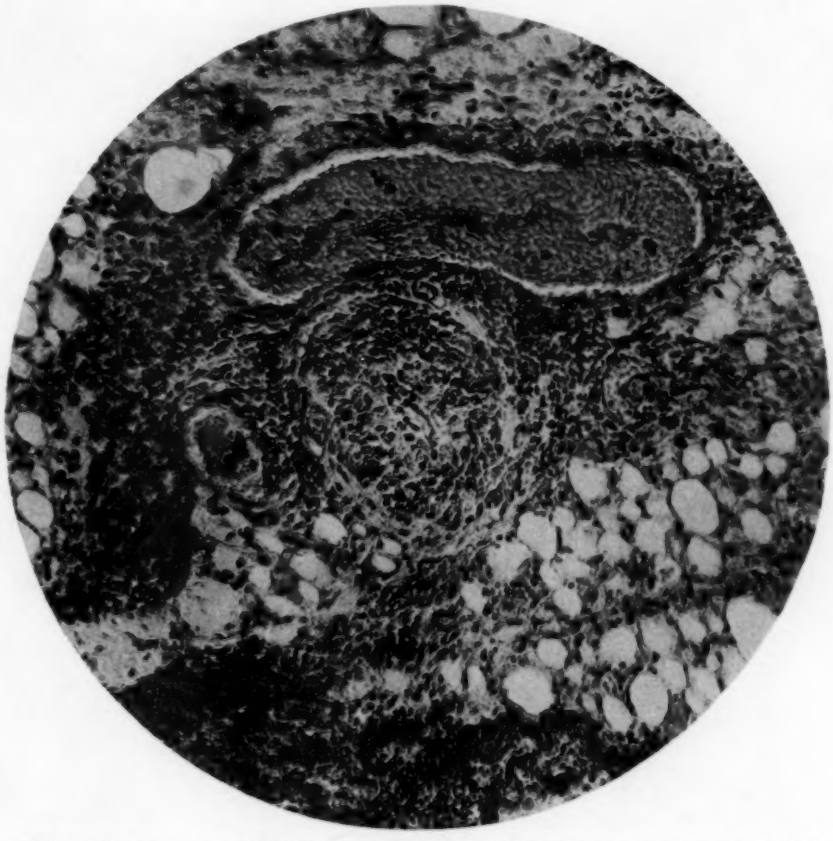

Fig. 1 (case 2).—Thickened veins and occluded arteries in mesentery; × 160.

ileocecal junction. The wall was extremely firm, measuring 1 cm. in thickness. At the ileomesenteric angle, several perforations were found. The mesentery leading to this portion of the intestine was thick and firm, and the thickest portion was definitely associated with the most extensive changes in the wall of the intestine. No ulcerations were found in the remainder of the gastro-intestinal tract. Additional findings were septic splenitis, bronchopneumonia and brown atrophy of the heart.

*Histologic Observations.*—Microscopic examination of a transverse section of mesentery leading to the ulcerated intestine revealed marked obliterative arteritis. Practically all of the medium-sized and small vessels showed extensive subintimal

connective tissue proliferation with reduction of their lumina to small slits. Some of the vessels were completely occluded, either by organized or by hyaline thrombi. Hyalinized fibrin was noted in the walls of some of the vessels. There were considerable subintimal deposits of connective tissue in the large vessels, but none were occluded. A collar of lymphocytes was present around some of the vessels. Many lymphocytes and endothelial leukocytes and a few polymorphonuclear leukocytes had infiltrated the supporting scarred fat. The intestinal wall was thickened

Fig. 2 (case 2).—Marked endarteritis in the vessels of the mesentery; × 160

because of marked scarring. Granulation tissue, heavily infiltrated with chronic inflammatory cells, covered the denuded mucosal surfaces. The histologic changes in the remaining organs were those resulting from sepsis.

Five hundred and seventeen grams of tissue was examined for mercury. The content of mercury, expressed as metallic mercury, was 3.88 mg.; 0.53 mg. was found in 83 Gm. of mesentery, and 3.35 mg., in 434 Gm. of intestine.

Case 3.—A white woman, aged 68, whose past history was unavailable, was seen in a moribund state by her physician in March, 1931. No history of her acute illness was obtainable. Physical examination revealed a profoundly ill, dehydrated, somewhat emaciated woman with a markedly distended abdomen. Red

blood was noted in both the stool and the vomitus. Attempts at giving enemas failed. Acute intestinal obstruction was diagnosed, but any operative procedure was deemed not advisable. Death occurred four days after the woman was first seen.

*Autopsy.*—Postmortem examination was limited to the contents of the abdomen. The pyloric end of the stomach and the terminal 6 feet (183 cm.) of ileum, with the cecum and a portion of the descending colon, were sent to the pathologic laboratory for study.

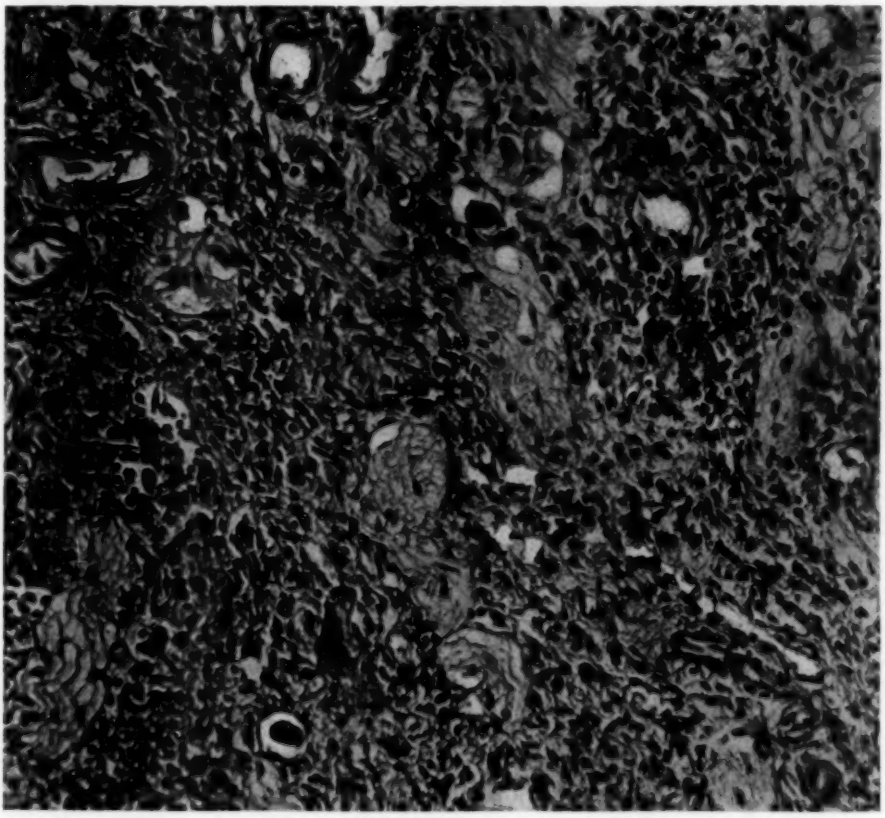

Fig. 3 (case 2).—Tissue from intestinal wall; × 220. Note fibrosis of small vessels, hyaline thrombi and atypical granulation tissue.

Examination of the stomach showed a superficial, somewhat irregular ulceration near the pylorus. The upper portion of the ileum appeared normal, but superficial diffuse ulceration of the mucosa of the lower portion was in evidence. Marked constriction of the colon was present, the total diameter being only 1.2 cm. The wall was extremely firm. Its entire mucosa was replaced by a homogeneous gray, firm, friable membrane.

*Histologic Observations.*—Microscopic section of the gastric ulcer revealed a denuded area of mucosa replaced by granulation tissue covered by fibrin. Polymorphonuclear leukocytes infiltrated the ulcer bed and underlying gastric wall. A

superficial portion of the mucosa of the lower part of the ileum that was necrotic and covered by fibrin heavily infiltrated with polymorphonuclear leukocytes presented the only histologic change in the ileum. Evidence of extreme injury was present in the colon. Practically the entire mucosa was necrotic. Many arteries in the submucosa contained fibrinous thrombi in variable amounts from those causing complete occlusion to small intimal deposits. The walls of many of the blood vessels consisted merely of irregular strands of homogeneous pink-staining tissue infiltrated with polymorphonuclear leukocytes. Hyaline thrombi were present

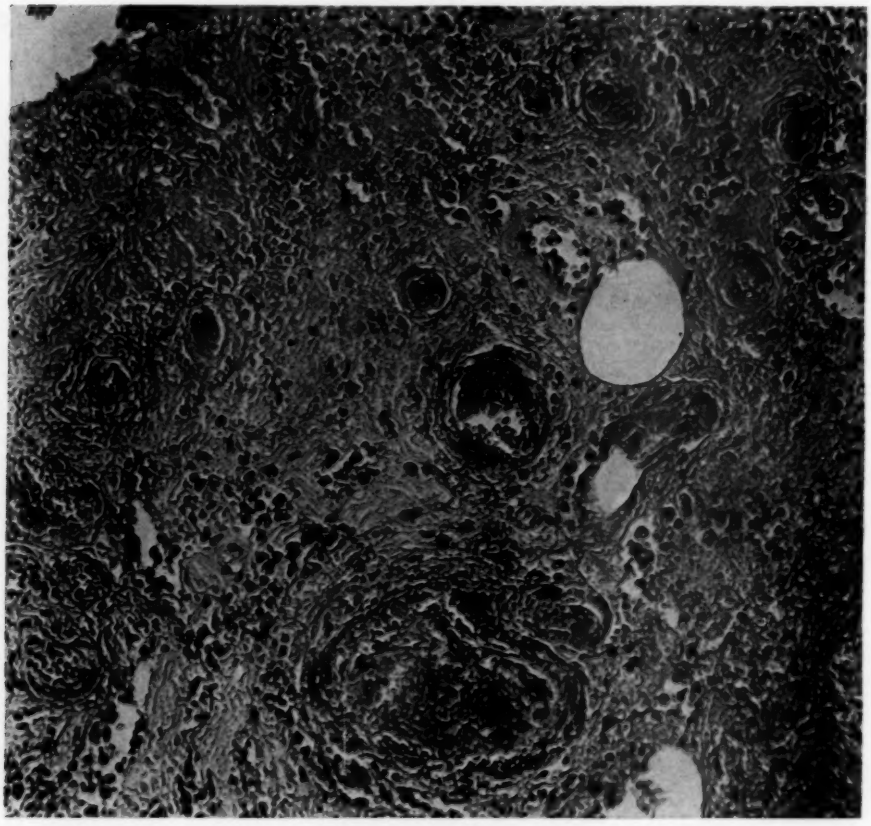

Fig. 4 (case 3).—Colon tissue; × 220. Note rather acute injury of vessels and thrombosis, as well as acute inflammation.

in many very small vessels. Edema was marked throughout the entire wall, with a diffuse infiltration by acute inflammatory cells.

## COMMENT

The mercury was isolated as the metal by Schreiber, according to the method evolved by Booth, Schreiber and Zwick for the determination of mercury in the presence of organic matter. In the second case, 517 Gm. of intestine and mesentery contained 3.88 mg. of mercury.

The mesentery removed, so far as this was possible, weighed 83 Gm. and yielded 0.53 mg. of mercury. The 434 Gm. of intestines yielded 3.35 mg. of mercury. The concentrations of mercury in the mesentery and intestine were 0.65 and 0.77 mg. of mercury per hundred grams, respectively. In the third case, the mercury found in 317 Gm. of tissue was 12.1 mg. The 42 Gm. of colon contained 9.9 mg.; the 45 Gm. of stomach, 0.2 mg., and the 230 Gm. of ileum, 2 mg. The concentrations in these various tissues were 23.5 mg., 0.44 mg. and 0.87 mg. per hundred grams of colon, stomach and ileum, respectively. The concentrations of the mercury in the tissues in the two cases in which mercury analyses were made paralleled the extent and the acuteness of the lesion described, with the exception of the mercury content of the gastric tissue, which was examined only in one case, and which showed a lower concentration of mercury than the other tissues in either case.

The question of whether mercury, like certain of the other metals, is a normal constituent of tissue may readily be raised. The literature

TABLE 1.—*Results of Analysis of Tissues for Mercury (Case 3)*

| Organ | Weight, Gm. | Metallic Mercury, Mg. |
|---|---|---|
| Colon | 42 | 9.9 |
| Stomach | 45 | 0.2 |
| Ileum | 230 | 2.0 |
| Total | 317 | 12.1 |

does not reveal much on this point. Traces of mercury are, at times, found in the tissues of persons who have had some of their teeth filled with amalgam. In two of our cases, mercury in some form was known to have been ingested. Schreiber stated that examination of tissues in cases in which it was certain that mercury had not been taken yielded no mercury.

The lesions produced in all three cases seemed to be primarily injuries to the walls of blood vessels—more prominent in arteries and small arterioles than in veins. There was proliferative endarteritis as well as thrombo-arteritis in the more acute cases. The extent of these changes was such that the intestinal walls had suffered markedly from ischemia.

One of the patients in our cases had chronic diarrhea. All three cases were eventually diagnosed carcinoma with perforation because of chronic intestinal obstruction and evidence of peritonitis.

It is striking that stomatitis and acute tubular nephritis, the lesions that we are wont to associate with mercury poisoning, are not integral parts of the clinical manifestations of this particular type of mercury poisoning. The lesions are primarily vascular. A limited portion, and not always the same portion, of the gastro-intestinal tract in the three

cases under consideration was diseased. This would imply the involvement of a limited portion of the vascular tree of a different part of the gastro-intestinal tract in each instance. The finding of mercury in tissues sixteen months after the ingestion has impressed us with the length of time during which this injurious agent may act. It will be interesting to see whether these divergent and disturbing features of the disease can be brought into accord by what is known of mercury and the reaction it causes in tissues.

The fate of mercury, when injected into the body or taken by mouth, is in part well known. The excretion by the way of the kidneys, the stomach, the mouth and the intestines with resultant lesions is well known in the more acute cases of mercury poisoning. We have learned from past experiences that whenever a new mercury compound is suggested for the relief of edema or as a genito-urinary antiseptic, and so on, the patient must be kept under observation for evidences of

TABLE 2.—*Circulation of Mercury: Amount of Mercury per Hundred Grams of Tissue After Intramuscular Injection of Various Compounds as Indicated*

| Tissue | Mercurium Benzoicum, 37.8 Mg. | Acidum Mercuric Salicylicum, 33.5 Mg. | Mild Mercuric Chloride, 48.0 Mg. | Metallic Hg (50% Oil Suspension), 154 Mg. |
|---|---|---|---|---|
| Liver | 0.49 | 1.16 | 0.37 | 0.65 |
| Kidney | 2.20 | 5.03 | 2.12 | 1.75 |
| Small intestine and feces | 0.39 | 0.55 | 0.19 | 0.29 |
| Large intestine and feces | 0.32 | 0.53 | 0.20 | 0.13 |

irritation of the kidneys, such as albumin and blood in the urine, or for gastro-intestinal injury evidenced by diarrhea and blood in the stool. The distribution of various mercury compounds in the tissues, which concentrate them energetically, may be noted in table 2, which was compiled from the work of Lomholt.

Cole, Gammel, Schreiber and Sollmann, as well as Lomholt and others, have found that after a short period of active elimination, the excreted mercury being only a small percentage of that injected, elimination falls rapidly to traces, which may persist day after day. Cole and his co-workers stated that a week after the injection of mercury salicylate, from 85 to 90 per cent remains unexcreted. With these facts before us, it is not difficult to believe that mercury may be found in the intestinal wall, which represents one of the concentration points of mercury, several years after ingestion.

Authors are well in accord that the gastro-intestinal tract is second only to the urinary tract in the excretion of mercury compounds. Cole and his co-workers stated that with mercury salicylate the excretion in the feces is about one-twelfth that of the urinary elimination. The literature in general is also quite clear that the excretion occurs along the

entire length of the gastro-intestinal tract. Bargen, Osterberg and Mann, however, found, in contrast with the general experience, that the colon of a dog had nothing to do with absorption and excretion of the mercury compounds that they studied. The opinion that the important reason for the concentration of mercury in the kidneys, liver and intestinal wall is for the purpose of excretion may be altered by this bit of evidence.

Another probable reason for the concentration of mercury along the gastro-intestinal tract was pointed out by Almkvist. He noted yellowish-black particulate matter in leukocytes and free in tissue in cases of mercury poisoning. He also found experimentally that hydrogen sulphide would precipitate the mercury in the tissues of the gastro-intestinal tract to the extent that yellowish flakes could be observed in the gross specimen. The fact has been pointed out that yellowish-black granules are found in such locations as the kidneys, where hydrogen sulphide probably does not play an important part in their formation. Elbe believed that the granules noted by Almkvist may be altered blood. The accumulation of mercury along the intestinal wall for excretion would seem to imply that the concentration should be regularly greater in that part of the gastro-intestinal tract more actively concerned with the excretory function in question. At this location, one would logically and regularly expect the more extensive lesions. This has not been true. Concentration of mercury between the large bowel and small bowel has varied as indicated in table 2. In our cases, the severe lesions were in the colon in one instance, while in the other two instances the lesions were confined wholly to the ileum. This would call for a factor in addition to that of concentration of the poison and injury to the tissue at the point of excretion. Almkvist's explanation would satisfy as to this variability of the amount of mercury and of the severity of the lesions along the gastro-intestinal tract. The precipitation of mercury and the extent of the lesion in a given case would be greatest at the point along the gastro-intestinal tract where the concentration of hydrogen sulphide chanced to be the more abundant at the time the mercury happened to be circulating in the blood.

It seems pertinent to consider the presence of gastro-intestinal lesions in the absence of tubular nephritis and stomatitis due to mercury poisoning. The fact that mercury may be excreted in the urine without renal lesion is well known. Rosenheim noted in his perfusion experiments that weak solutions of mercury compounds caused vasoconstriction, while stronger solutions not only caused vasoconstriction, but irritated the renal parenchyma and caused diuresis. On the other hand, patients receiving mercury therapy frequently have diarrhea and

even blood in the stool in the absence of stomatitis or nephritis. Again, whether Almkvist's interpretation of his yellowish-black granules is the correct one or not, there seems to be a factor that operates along the gastro-intestinal tract rendering the concentration of mercury in mercury poisoning largely a matter of chance, in the more chronic types of mercury poisoning. It would be possible, under such conditions, to obtain high concentrations of mercury in various parts of the tract without either nephritis or stomatitis.

Information on what happens and on the sequence of events in the production of the lesion can be gathered from the literature. First, the poison must be concentrated in a certain locality in order to produce a lesion. The corrosive action of heavy metals may be effective at the point of application, where the concentration may be great, or at the point where it accumulates for excretion. Added to this, one has a second factor, which may be the precipitation of mercury pointed out by Almkvist. Niklasson and Santesson indicated, as a result of their investigations, that not only is the presence of mercury in the tissue necessary, but it must be in ionic form to be injurious to tissue. The observations on vasoconstriction made by Rosenheim in his perfusion experiments have also been pointed out by Elbe, Weiler, Natus, Kaufmann and others. The sequence of effects of mercury on vessels and contained blood is: constriction, dilatation, constriction, stagnation and diapedesis of red blood cells. This is virtually an infarction without complete occlusion of the vessel. Kaufmann noted that the stasis resulted in hyaline thrombi in vessels. He believed that the stasis, the hyaline thrombi and the action of bacteria are sufficient to explain the changes found. However, the destruction of intima, the formation of mural thrombi and the injury to the wall of the vessel in our third case are precisely the changes described by Wolff as occurring when he injected mercuric chloride directly into the veins of rabbits. It would seem from the evidence presented that in mercury poisoning there is an action peripherally on the vasomotor mechanism at the point where the mercury is concentrated, plus the irritant action of a foreign body, as well as the corrosive action of an ionizable mercury compound, all acting concurrently on the tissue concerned. Naturally, after the tissue is thus devitalized, the factor of infection is added.

## SUMMARY

Three cases of a peculiar type of mercury poisoning are described. The lesions were primarily vascular. A limited portion of the gastro-intestinal tract was involved in each case. The same part of the intestinal tract was not involved in any two of the cases. No stomatitis or nephritis was noted.

The peripheral action of mercury on the vasomotor mechanism and the corrosive action of ionizable mercury compounds, as is pointed out in the literature on experimental mercury poisoning, are sufficient, with the additions of the action of mercury as a foreign body and the unavoidable secondary infection, to account for the lesions found.

Chronic intestinal obstruction with evidence of perforation should prompt one to consider the possibility of mercury poisoning.

A postmortem examination that shows primary vascular injury to a limited portion of the gastro-intestinal tract should suggest mercury poisoning as a possible cause until it can be excluded by careful chemical analysis for mercury.

# EXPERIMENTAL PATHOLOGY OF THE LIVER

## VIII. EFFECTS OF CARBON TETRACHLORIDE ON THE NORMAL AND ON THE RESTORED LIVER AFTER PARTIAL HEPATECTOMY

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Since carbon tetrachloride has proved of value as an anthelmintic in clinical medicine,[1] its toxic effects should be thoroughly understood. Experimental studies have shown that the liver is highly susceptible to the drug, and that repeated injections of it may induce cirrhosis.[2] In order to produce marked cirrhosis, however, carbon tetrachloride must be given for a considerable period; with sufficient intervals between injections, regeneration may go on without any permanent changes being induced in the organ. Such regeneration of hepatic parenchyma is probably similar to that which takes place after partial removal of the organ.[3] Regeneration after partial hepatectomy, however, may be repeated indefinitely, whereas in cases of continuous injury to the liver, such as that induced by carbon tetrachloride, complete regeneration finally fails to take place and connective tissue proliferation ultimately produces cirrhosis. In partial destruction of the lobules of the liver by such a toxic agent as carbon tetrachloride, replacement occurs at the site of injury and a new hepatic lobule is regenerated. On the other hand, the growth of the remnant of liver, after partial hepatectomy, is a compensatory hyperplasia in which an attempt is made to restore the original volume of hepatic tissue. The term regeneration as used in this report includes recovery following poisoning by carbon tetrachloride, and the term restoration denotes changes that ensue following partial removal of the organ.

Since restoration of the liver occurs so rapidly following partial removal of the organ, in which no doubt a return to a primitive or an embryonic condition may take place, I wished to know whether the

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From the Division of Experimental Surgery and Pathology, the Mayo Foundation.

1. Lambert, S. M.: J. A. M. A. **80**:526, 1923.

2. (*a*) Bollman, J. L.: Proc. Staff Meet., Mayo Clin. **5**:116, 1930. (*b*) Docherty, J. F., and Burgess, E.: Brit. M. J. **2**:907, 1922. (*c*) Gardner, G. H., and others: Bull. Johns Hopkins Hosp. **36**:107, 1925. (*d*) Lamson, P. D., and Wing, R.: J. Pharmacol. & Exper. Therap. **29**:191, 1926.

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newly restored liver would react more or less intensively to carbon tetrachloride than the normal liver. Accordingly, the investigation was conducted along three lines: (1) the effect of carbon tetrachloride on the normal liver; (2) the effect of carbon tetrachloride during restoration of the liver, when administered prior to partial removal, and (3) the effect of carbon tetrachloride during restoration of the liver, when administered after partial hepatectomy. White rats were used in the study.

## EXPERIMENTAL METHOD

In most of the experiments 0.25 cc. of carbon tetrachloride was given by stomach tube twice a week. As the effects of different diets on the entire process of hepatic injury have been emphasized,[4] the rats were maintained on an adequate diet consisting of corn meal, linseed oil meal, crude casein, alfalfa meal, salt, calcium carbonate and powdered skim milk.

All operations of partial hepatectomy were performed under aseptic technic and ether anesthesia, and sections were fixed in 10 per cent formaldehyde, stained with hematoxylin and eosin, scarlet red, van Gieson's stain and Mallory's stain for connective tissue. Bile capillaries were stained with the technic of Otani.[5] For the observation of certain cytologic details, especially mitochondria, sections were treated according to the silver and gold method of del Rio Hortega. Other staining methods for mitochondria were occasionally used for comparison.[6]

## OBSERVATIONS

In order to determine the effect of a single injection of carbon tetrachloride on the liver, 0.25 cc. of the drug was given by mouth to each of a series of rats. At intervals after the administration, a lobe of the liver was removed for examination. Within three hours, the liver appeared to be slightly injured. Besides congestion, the central areas of the lobules were paler than at the periphery. In some cells, the protoplasm was cloudy, the nuclei were irregular, and the fat content, in those in the middle zones of the lobules, had increased. Granular mitochondria appeared in cells of the central zone and in the vacuolated cells of the middle zone; in the periportal zone, however, the mitochondria were normal in that they were rodlike and evenly distributed throughout the cells.

At six hours, swelling of the cells of the liver was general in the central areas, and fatty degeneration and pyknotic nuclei were common (fig. 1). The endothelium of the central vein was swollen, often desquamated and frequently ruptured. In the portal areas, the cells were normal, whereas in the middle zone there was a ring of clear, vacuolated cells filled with fat, often without any visible protoplasm or

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5. Otani, Sadao: Proc. New York Path. Soc. **26**:2, 1926.

6. Gough, J., and Fulton, J. D.: J. Path. & Bact. **32**:765, 1929.

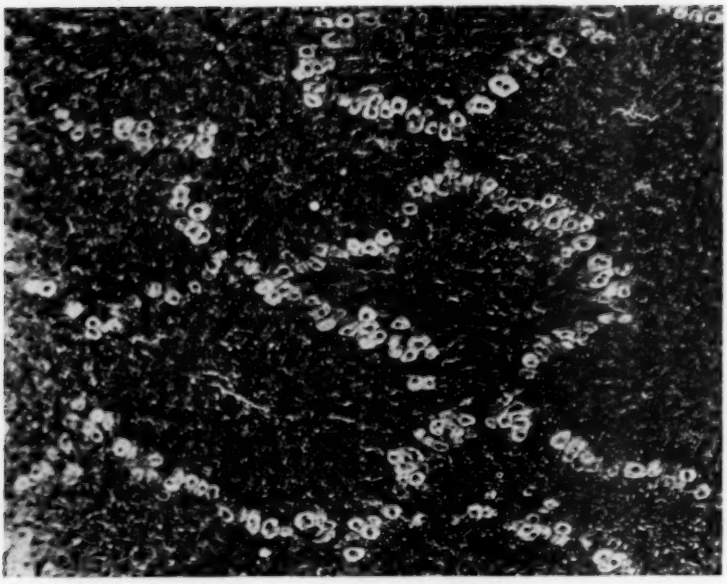

Fig. 1.—Liver of white rat six hours after oral administration of 0.25 cc. of carbon tetrachloride.

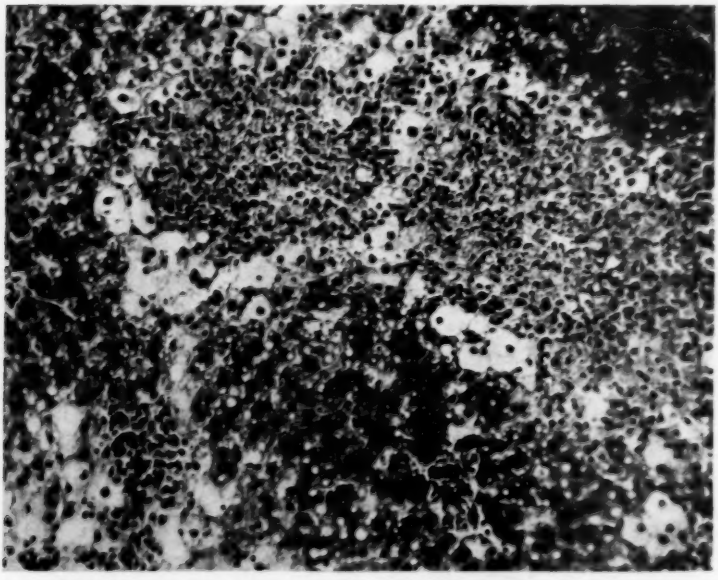

Fig. 2.—Liver of white rat twenty-four hours after oral administration of 0.25 cc. of carbon tetrachloride.

nuclei. Small droplets of fat occurred in the cells of the central zone, but they were practically absent from the cells at the periphery of the lobule. It was estimated that from 25 to 50 per cent of the parenchyma of the liver was loaded with fat. The mitochondria had disappeared from the large fat-containing cells of the middle zone, and from several cells in the central zone. In other cells of this zone, the mitochondria were degenerating, coagulated into clumps or thick granules around the nucleus (perinuclear condensation); in the remaining part of the cell, the protoplasm was coagulated and grossly granular. At the periphery of the lobule, however, the mitochondria remained rodlike and evenly distributed throughout the hepatic cells.

The maximal injury to the liver apparently was reached twenty-four hours after the administration of a single injection of the drug (fig. 2). All cells of the lobule were distended with either small or large clear fat vacuoles, and necrosis was marked in the central zones. Central veins were destroyed, and erythrocytes were widely distributed throughout the sinusoids. Lymphocytes, polymorphonuclear cells, mononuclear phagocytic cells, monocytes with horseshoe-shaped nuclei and many eosinophilic leukocytes had invaded the necrotic area. Kupffer cells had increased in number and had migrated toward the center of the lobule. Globules of fat, very irregular and often confluent, filled the central and middle zones, while at the periphery the fat droplets were more discrete and more uniform in size, and were within the cytoplasm of the hepatic cells. In some sections the veins were largely distended with fat. The mitochondria at twenty-four hours were normal in the periportal zone, but appeared as short, thick rods elsewhere, assuming a periglobular distribution (fig. 3). This arrangement of the mitochondria is probably due to a mechanical effect induced by the vacuolation of the protoplasm, for the mitochondria were pushed around the nucleus and against the cell membrane by the fat vacuoles. Nearer the central veins, the mitochondria were more infrequent, and they were entirely absent in the central zones, where there were only reticulum, fragmented nuclei and various infiltrating cells. Mitotic figures were identified at this stage in the periportal zone or even among the fatty cells, and indicated that an attempt at regeneration was in progress.

Two days after administration, the injury to the liver was still marked, although there was less fat at the periphery of the lobule, and the cells bordering on the portal spaces were again more nearly normal (fig. 4). The central vein had disappeared, and granular débris of coagulated protoplasm and hyaline degeneration represented all that remained of the central zones of the lobules.

After four days, the necrosis was restricted to a small central area, sharply demarcated from the remainder of the lobule. The fat content was reduced and restricted to the middle zone, and active phagocytosis

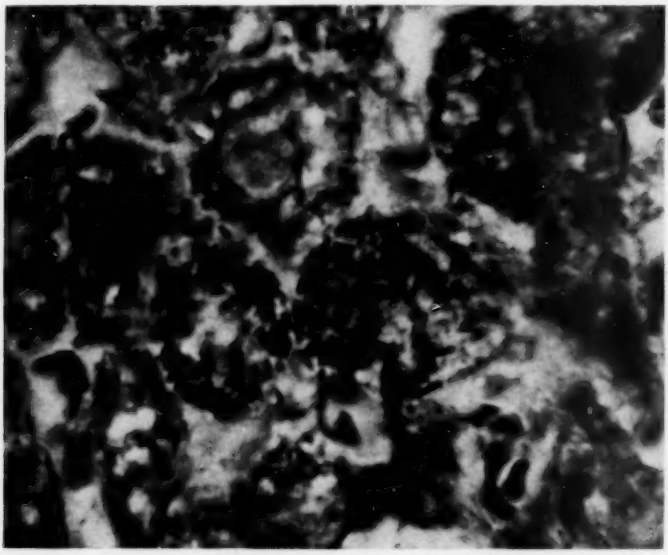

Fig. 3.—Concentration of mitochondria in hepatic cell of liver of white rat twenty-four hours after oral administration of 0.25 cc. of carbon tetrachloride.

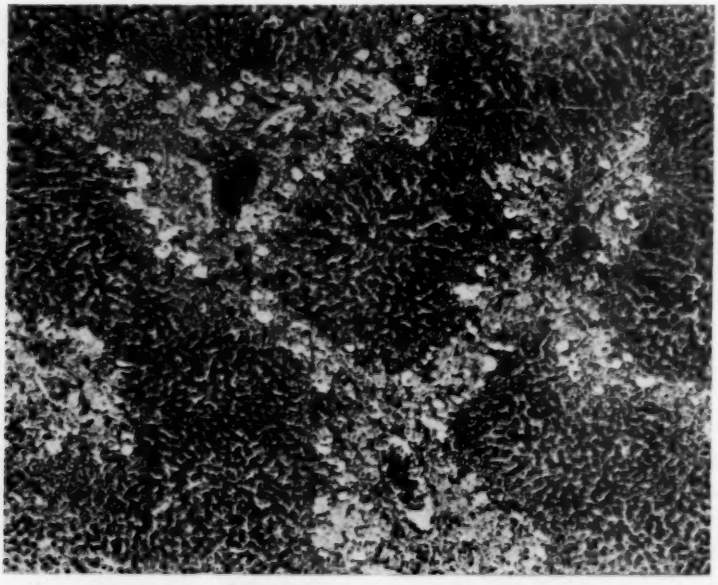

Fig. 4.—Liver of white rat two days after oral administration of 0.25 cc. of carbon tetrachloride.

had eliminated most of the cellular débris. There was considerable activity of the Kupffer cells, and the cells of the mesenchyme were still preponderant in the central zone. The mitochondria were again normal after four days, and after one week a few necrotic cells with some infiltrating lymphocytes remained in the center of the lobules. The walls of the central veins were incomplete in most instances, although their restoration from the uninjured portion of the endothelium was in progress. Necrosis was often sufficiently extensive completely to destroy the entire vein, so that a new endothelium developed from the cells of the mesenchyme which filled the central zones. The development of a definitely organized vascular channel was preceded by clefts or spaces within these infiltrating cell masses, and subsequently certain of these cells gave rise to attenuated protoplasmic processes which formed a clearly delineated wall, the endothelium of the new central vein. These cells of the mesenchyme were probably embryonic, and the organ may revert to embryonic principles in producing from undifferentiated mesenchyme a specialized and differentiated endothelium. Under normal conditions, these mesenchymal cells are usually restricted to the portal spaces, but the necrotic zone around the central veins induced mobilization in order to phagocytose the débris and to assist in the reconstruction.

It was clear from this preliminary study that injury to the hepatic lobule was microscopically evident in three hours following a single oral administration of 0.25 cc. of the drug. Destruction spread from the central portion toward the periphery and reached a maximum at twenty-four hours, when practically the entire lobule was involved.

With larger doses of 0.50, 0.75 or 1 cc. of carbon tetrachloride the injury to the lobule was far more extensive. Instead of a central area of coagulation and hyaline degeneration, there was a uniform diffuse lesion with cloudy swelling, pyknosis and granular and fatty degeneration over the entire lobule. Following a single injection of 0.75 cc., normal hepatic tissue was not identified after two days. Repair following larger doses of the drug took place more slowly, and the degree of injury was not proportional to the amount injected. A very large dose, such as 2 cc., killed the animals by a functional disturbance without extensive anatomic lesions in the liver. In the same way, the addition of alcohol to the drug increased its toxicity without inducing extensive pathologic lesions. The gross appearance of the liver rather closely conformed to the histologic detail. When the liver was injured by carbon tetrachloride, the organ was swollen, soft and friable. Central necrosis was indicated, grossly, by a delicate yellow tracing with distinct markings over the surface. The liver was yellowish brown or frequently, in cases of extreme injury, entirely yellow. Regeneration, however, induced a normal macroscopic appearance. As far as either

the macroscopic or the histologic appearance was concerned, there was no difference between the right and the left lobes of the liver.

In another series of rats, injections of 0.25 cc. of carbon tetrachloride were given twice a week for varying periods. From three to six injections produced lesions of the same sort as a single injection. Areas of hyaline degeneration and necrosis were invaded by erythrocytes and by excessive mononuclear infiltration, and they were surrounded by cells that were often distended by a single large fat vacuole and on the periphery by cells containing smaller vacuoles. The endothelium of the central veins was partially or entirely destroyed, and the central vein often appeared as a space surrounded by a thick layer of these cells of infiltration. Occasionally both the central and the portal areas became contiguous, and the necrosis, which was actually central in origin, resembled a periportal lesion.

The pathologic condition of the organ was not always proportional to the number of injections given; neither was it indicative of the prognosis for the life of the animal. The liver of a rat that received three injections and was killed four days later might be more severely injured than that of a rat receiving six injections that was killed two days later. In the same way, a rat that died spontaneously might have a better liver histologically than a rat killed while in good general condition at a longer interval after the injection. There was a marked increase in the number of bile ducts following repeated injections, often more apparent than real. Many groups of epithelial cells, often without lumen, as well as buds of cells indicated a real proliferation of new bile ducts. In cases of slight reaction, proliferating bile ducts were restricted to the portal spaces, but whenever an area of central necrosis reached a portal space, the bile ducts proliferated into this extensive necrotic zone.

The demonstrable fat content of these injured livers was very high. Fat globules were found even in the cells undergoing mitosis, and cells around the portal spaces were speckled with small globules of fat. The numbers of fibroblasts in the zones of infiltration suggested early development of connective tissue with fibrosis. With special staining technic, layers of connective tissue were identified around the central vein, and fibers followed the axis of the bands of infiltration into the necrotic zones.

After from ten to thirty injections, however, the connective tissue reactions had increased (fig. 5). There was definite fibrosis, which disturbed the usual lobulation and divided the parenchyma into small separate and distinct islands of pseudolobules. These islands of hepatic cells, largely vacuolated with fat, were encircled by fibrous tracts.

Repeated poisoning appeared to exhaust and destroy the regenerating power of the hepatic parenchyma and at the same time stimulated

the mesenchyme to more active proliferation. Regeneration and cirrhosis were not secondary to each other, but represented two separate reactions produced by the toxic agent. The capacity for regeneration and the extent of cirrhosis following repeated injections were inversely proportional to each other. Whereas regenerative capacity decreased, so that the liver lost its replacement power, the fibrous reaction rapidly increased and produced marked cirrhosis.

Following repeated injections, livers were macroscopically large, with yellow tracings throughout. They were no longer soft, but exceedingly firm and hard, and presented a hobnail roughness on the surface.

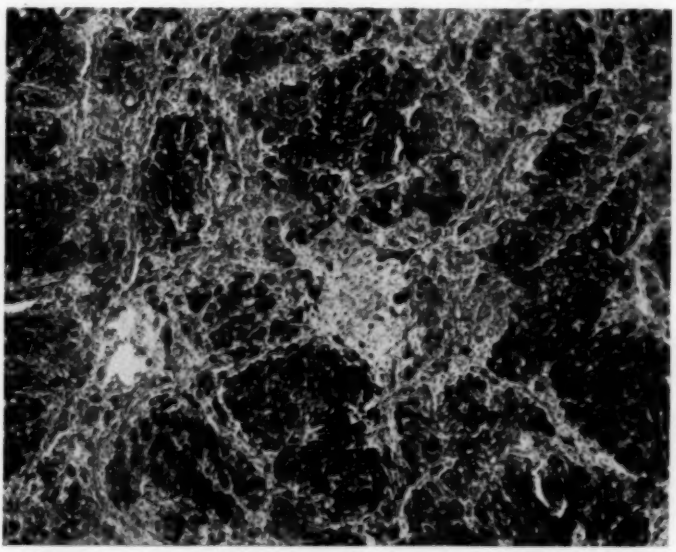

Fig. 5.—Liver of white rat after oral administration of eleven doses of 0.25 cc. of carbon tetrochloride (two doses a week).

The macroscopic and histologic lesions at this stage bore the first evidence of the typical atrophic cirrhosis with circulatory disturbance which the frequent repetition of injury from carbon tetrachloride brings about in the liver.

*Effects of a Single Dose of Carbon Tetrachloride Before Partial Hepatectomy.*—In order to study the combined effect of chemical injury and partial removal, 0.25 cc. of carbon tetrachloride was given to each of a large number of rats. Twenty-four hours later, when the lesion was extensive and the regenerative process had begun, two lobes of the liver were removed. At intervals after the operation, three rats were killed, and the remnants of liver were removed for study.

Twenty-four hours after the operation, or two days after the carbon tetrachloride was given, the lesions of central necrosis were as extensive as those occurring twenty-four hours after a single dose of carbon tetrachloride had been given without partial hepatectomy. The types of injury to the cytoplasm, the nuclei and the mitochondria were essentially like those described. The lesions were not definitely restricted to the center of the lobule, and degenerating cells with pyknotic nuclei occurred throughout the lobule.

Two days after the operation, or three days after the carbon tetrachloride was given, the injury was comparable to that seen two days after the administration of the drug alone. It would seem that the detoxifying factor which may exist in the normal liver was reduced in the animals operated on, for the organ was less resistant and the process of recovery retarded. This retardation, however, was only manifest during the first two or three days, for on the fourth day after the operation the liver had overcome this first inhibition and was in active regeneration. At one week, repair of the liver was as marked in partially hepatectomized animals as in those clinically injured. It is of interest that in the livers in a state of restoration, numbers of fibroblasts among the infiltrating cells had given rise to connective tissue fibers around the central veins, so that after this first brief period of delay restoration progressed with its sequence of hypertrophic nuclei, mitosis and nests of hematopoietic cells, budding bile ducts and marked mesenchymal and reticulo-endothelial activity. It seems that the combined action of restoration and regeneration had induced more intense activity of the mesenchyme and especially of the Kupffer cells.

*Effects of a Single Dose of Carbon Tetrachloride After Partial Hepatectomy.*—In order to study the effects of carbon tetrachloride on the liver during restoration, we gave a single injection of the drug to several groups of animals at varying intervals after the surgical removal of about 65 per cent of the liver.

The first group included animals operated on that received the drug before the hepatic remnant had regained its normal weight and volume (that is, before two weeks after partial removal). It is difficult to draw any definite conclusion from these experiments concerning the susceptibility of the organ to the drug, since the substance of the liver was only a third or a half of the original normal amount. The injection was in a measure equivalent to the administration of a double or a triple dose.

The animals of the second group received carbon tetrachloride after the remnant of liver had attained its normal volume, but before restoration was complete histologically (that is, between the second and fourth weeks after partial removal). In these animals the liver was a new, rapidly growing parenchyma with high metabolic activity, and it

possessed at least some embryonic qualities. Rather striking results were obtained in these experiments.

Twenty-four hours after 0.25 cc. of carbon tetrachloride was given to these animals, central necrosis and fatty degeneration were far less extensive than in the normal liver that had been subjected to injury (fig. 6). The nuclei were pyknotic, and there was slight round cell infiltration in the region. The central veins were incomplete or defective, and hemorrhage had occurred. Fat globules filled the cells of the middle zone, but the periportal zones were free, and the portal spaces were intact. This injury of twenty-four hours in the restored liver was similar to a six hour lesion in the normal liver. The hepatic cells were

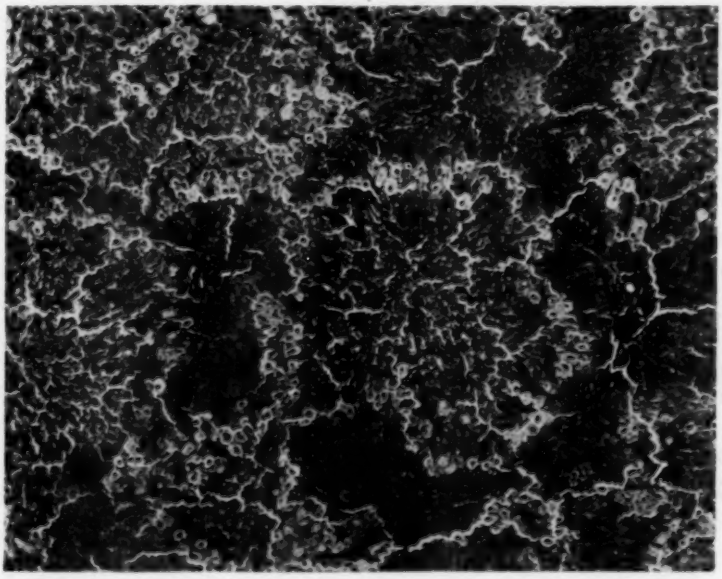

Fig. 6.—Liver of white rat, four weeks after partial hepatectomy and twenty-four hours after oral administration of 0.25 cc. of carbon tetrachloride.

large, and a fair number of mitotic figures were visible all over the lobules. Normal rodlike and granular mitochondria occurred in the cells at the periphery and in the middle zone, and as a whole the lesion was less extensive, and regeneration and repair were completed within a short period.

Unquestionably, there was a significant difference in the effect of the toxic agent on the normal and on the newly restored liver. The latter was more resistant to the drug and seemed to have a higher detoxifying ability. Several weeks after partial hepatectomy, the liver might again be considered normal, in that the effects of carbon tetrachloride were essentially identical with those of the normal liver.

COMMENT

It is quite clear that the cirrhosis produced by carbon tetrachloride cannot be caused by necrosis, for the production of connective tissue, after a certain number of doses of carbon tetrachloride, is not dependent on the extensive necrosis. Fibrous tissue was produced with very small repeated injections, which caused little necrosis, but it did not appear in a liver that had been almost destroyed by one massive dose. A slight connective tissue reaction occurred following a single injection of carbon tetrachloride, but it increased as the stimulation was repeated more frequently. Van Heukelom,[7] in 1896, demonstrated that necrosis and cirrhosis are independent of each other, although they may be induced by the same pathogenic factor. Cirrhosis, in the later stages, can impair the vitality of hepatic cells by compression, so as to cause necrosis.

The early localization of fat in the hepatic lobule after the administration of carbon tetrachloride may be contrasted with the observations of Fiessinger [8] on periportal lesions induced by chloroform. The areas of vacuolated cells appearing six hours after the administration of carbon tetrachloride and persisting for at least twenty-four hours were not observed after the administration of chloroform,[9] phosphorus [10] or any other toxic agent.[11] With a few exceptions, all authors describe injury from chloroform as central,[12] and injury from phosphorus as periportal. As was suggested by Loeffler,[13] a poorer blood supply may serve to explain the localization of the fat in the middle zone of the lobule. However, I did not observe vasoconstriction, and the stasis of the blood described by Loeffler as central after chloroform poisoning was more uniform over the entire lobule following carbon tetrachloride poisoning. Finally, both the central necrosis and the central origin of the cirrhosis after the administration of carbon tetrachloride rather nullify the opinions of Noël and Rosier,[14] who explained the periportal action of any toxic agent by the histophysiology of three zones of the lobule.

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7. van Heukelom, Siegenbeck: Beitr. z. path. Anat. u. z. allg. Path. **20**: 221, 1896.

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12. Loeffler, L., and Nordmann, M.: Virchows Arch. f. path. Anat. **257**:119, 1925.

13. Loeffler, L.: Virchows Arch. f. path. Anat. **265**:41, 1927.

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In cases of severe injury I found large amounts of fat in the hepatic veins and in the bile ducts coincident with the postmortem observations of MacMahon and Weiss.[15] In a case of carbon tetrachloride poisoning, these authors described the presence of many fat globules in the central and middle zones of the lobules of the liver, as well as in the hepatic veins. Fat even occurred in the blood of the right side of the heart, and the larger pulmonary arteries contained as much as 60 per cent fat.

The reactions of mitochondria to carbon tetrachloride correspond to the description of Mayer, Rathery and Schaeffer [16] and Okushi;[17] they described protoplasmic cytolysis and chondriolysis and homogenization. Mitochondria are most labile and show the earliest effects of the injury, but before they disappear completely, they prove more resistant than their initial action would indicate.

The proliferation of bile ducts and new parenchyma after partial hepatectomy and chemical destruction of the liver, together with the appearance of infiltrating cells, indicates a return to an embryonic condition. Budding and branching bile ducts produce a tubular type of gland, and these cells may gradually transform into parenchymal cells. Many authors admit the participation of the bile ducts in the regeneration of hepatic cells. This procedure, however, plays a secondary part, for mitotic figures in the parenchyma account for the production of many new cells, whereas, contrary to Ponfick [18] and others, mitotic figures were not observed in the epithelial cells of the budding bile ducts. But under conditions of severe injury, such as several doses of carbon tetrachloride may induce, mitosis was never seen, and it may be that hepatic parenchyma is maintained by the actively proliferating biliary epithelium.

## SUMMARY AND CONCLUSIONS

The purpose of this investigation was to determine whether the properties of the restored liver after partial removal were different from those of the normal organ. The effect of carbon tetrachloride on the restored liver was compared with its effect on the normal organ. It was found that when a single administration of 0.25 cc. of carbon tetrachloride was given by stomach tube to a normal rat, weighing from 150 to 200 Gm., central necrosis and fatty degeneration of the liver ensued. The maximal lesion was reached after twenty-four hours, and the liver was completely regenerated after two weeks. Repeated injections, however, induced typical cirrhosis.

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15. MacMahon, H. E., and Weiss, Soma: Am. J. Path. **5**:623, 1929.

16. Mayer, A.; Rathery, F., and Schaeffer, G.: J. de physiol. et de path. gén. **16**:581, 1914.

17. Okushi, Ichiroemon: Tr. Jap. Path. Soc. **18**:145, 1928.

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From the standpoint of the effects of carbon tetrachloride following partial removal of the liver three conclusions were apparent: 1. When chemical injury preceded partial hepatectomy, recovery was greatly retarded. 2. When chemical injury was induced from two to four weeks following partial removal, the lesion was far less marked and recovery ensued far more rapidly than in the normal liver following administration of the drug; the restored liver appeared to be considerably resistant to the toxic influence of the drug. 3. When chemical injury was induced two months after partial removal, the extent of the lesion was more or less identical with that in a normal liver following administration of carbon tetrachloride.

# MORPHOLOGY OF THE INFLAMMATORY DEFENSE REACTIONS IN LEUKEMIA

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Since the cells of an exudate are chiefly derived from the circulating blood, it is to be expected that profound changes in the cellular composition of the blood will manifest themselves in the morphology of the inflammatory defense reactions. Thus, in spontaneous or experimental agranulocytic conditions, inflammation is characterized by the severity and the predominance of the alterative process and the lack of cellular response, and though histiocytes and lymphocytes occasionally accumulate about the necrotic areas, they are unable to compensate for the loss of the granulocytes (Rotter,[1] Mönckeberg,[2] Silberberg,[3] Winternitz and Hirschfelder [3a] and others). If only a few granulocytes are left, they are quickly drawn to the focus of inflammation and help in localizing it (Silberberg).

Histologic studies on inflammation in leukemia are few, and the observations recorded are contradictory. The finding most frequently noted is that of the predominance of polymorphonuclear leukocytes in the exudate of cantharidin blisters in cases of lymphatic leukemia (Litten,[4] Neumann,[5] Sonnenfeld and Leffkowitz [6] and others). Askanazy [7] and Naegeli [8] described neutrophilic leukocytes in the gangrenous lesions of the oral cavity in acute leukemia. Rodler-Zipkin [9] studied a case of acute large-celled lymphatic leukemia in which there was a suppurating sinus in the region of the left knee, and found in the granulation tissue lining this sinus many leukocytes. According to Naegeli, the appearance of granulocytes in inflamed areas in cases of

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From the Department of Pathology of the Cook County Hospital and the Uihlein Memorial Laboratory of the Grant Hospital.

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2. Mönckeberg, J. G.: Verhandl. d. deutsch. path. Gesellsch. **16**:150, 1913.
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3a. Winternitz, M. C., and Hirschfelder, I. B.: J. Exper. Med. **17**:657, 1913.
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lymphatic leukemia depends on the presence of remnants of granulopoietic tissue in the bone marrow. If the bone marrow is completely devoid of granulocytes, not a single pus cell can be detected in the foci of inflammation. This was the case in an acute lymphoblastic leukemia reported by Schultze [10] in which there were shown numerous hemorrhagic blisters of the skin. The blisters contained many large mononuclear cells and streptococci, but pus cells were absent. A similar substitution of neutrophilic leukocytes by leukemic cells in acute inflammation was observed by Dionisi,[11] who concluded from his findings that the characteristic elements of lymphemic blood were able to migrate through the wall of the blood vessels if the leukemic organism was confronted with an inflammation. Bickhardt,[12] too, stated that the leukemic patient reacts to an inflammatory irritation in the same manner as a normal person, the pathologic blood cells, however, substituting the polymorphonuclear leukocytes in the exudate.

In discussing the relations between inflammation and leukemia, one has to take into consideration the fact that an intercurrent infection often influences the blood picture and also the cellular composition of the blood-forming organs, establishing more or less normal conditions (Dock,[13] Hirschfeld,[14] Naegeli [8] and others). The leukemic organism does not seem to have lost the ability to produce normal blood cells (Hirschfeld), and this ability can be awakened by bacterial toxins (H. F. Müller [15]).

Little attention has so far been given to the productive inflammatory processes in leukemia save the combination between leukemia and tuberculosis, which will be discussed in a later publication. Since the morphology of leukemia is characterized by a profound change in the blood-forming potencies of the mesenchyma, it will be of special interest to investigate how this abnormal mesenchyma reacts to an inflammatory stimulus. Does it reveal these abnormal potencies when irritated, or does its reaction not differ from that of normal mesenchyma?

During the last three years I have collected among thirty cases of leukemia ten in which, at autopsy, inflammatory lesions were found, and in which the autopsy was done so shortly after death as to secure perfect fixation. The histologic descriptions are based mainly on

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15. Müller, H. F., cited by Hirschfeld.[14]

material fixed after Helly and Maximow and stained after Giemsa and fixed with a solution of formaldehyde U. S. P. (1:10) and stained for stable oxydase.

### LYMPHATIC LEUKEMIA

CASE 1.—*Confluent Bronchopneumonia in a Case of Subacute Lymphatic Leukemia.*—A white boy, aged 6, had been suffering from profuse night sweats and a frequent, nonproductive cough for two years. Seven weeks before admission to the hospital, illness developed following the extraction of a tooth. The mother noticed that the child's abdomen became larger, and that he looked pale. Numerous bluish, pinpoint-sized to nickle-sized spots appeared all over the body and faded in two weeks. There was a persistent discharge from the nose with the formation of thick crusts.

On admission, the patient's temperature was 101.6 F., the pulse rate was 100, and the respiratory rate was 24. The lymph nodes on both sides of the neck, especially on the right side, and in both axillae and groins were bean-sized, discrete and soft. The breath sounds throughout the lungs were exaggerated, and a rumbling systolic murmur was heard over the pulmonary area. The lower edge of the liver could be felt two fingerbreadths below the costal arch. The spleen was not palpable.

The erythrocyte count was 1,260,000; the hemoglobin content (Newcomer) was 22.5 per cent; the white blood cell count was 9,725, with lymphoblasts 74.5, lymphocytes 24.5 and neutrophils 1 per cent. The platelet count was 62,000. Marked anisocytosis and poikilocytosis were present; there were 6 normoblasts per two hundred white cells.

The child remained in the hospital for six weeks, during which the white count fluctuated between 3,200 and 31,000.

Autopsy: There was slight hyperplasia of the cervical, axillary, inguinal, peripancreatic, peribiliary, periaortic and mesenteric lymph nodes; the largest of the nodes measured 15 by 15 by 10 mm. The spleen weighed 155 Gm. and was moderately firm; the pulp was bright purple-red with small follicles. The liver weighed 1,070 Gm.; the heart, 145 Gm. Severe generalized anemia was present. Extensive hemorrhages were found about and in both kidneys; the kidneys weighed 590 Gm. Other changes were: severe fatty changes of the myocardium and liver; petechial hemorrhages in the skin, pericardium, endocardium, renal pelvis, suprarenal cortex and urinary bladder; hydropericardium; hydrothorax of the left side; focal bronchopneumonia of the left lower pulmonary lobe, and confluent bronchopneumonia of the right lower lobe.

Histologic Observations: Microscopic examination of the organs showed the typical picture of large-celled lymphatic leukemia with dense infiltrations in the splenic pulp, in the periportal septums of the liver and in the stroma of the kidneys and pancreas. There were smaller infiltrations in the lung and underneath the epicardium and endocardium. The lymph nodes were almost exclusively composed of the large cells, and there were only a few remnants of the secondary follicles. In the spleen, the malpighian bodies could be distinguished from the pulp, since they were formed by small lymphocytes. The bone marrow was a uniform accumulation of large lymphoid cells. The type cell of all the infiltrations was a cell about from 12 to 14 microns in diameter. The nuclei were round or slightly indented, contained evenly distributed small chromatin granules and were surrounded by scanty light blue cytoplasm, which was free from oxydase granules. These cells were mixed with a varying, but usually small number of small lymphocytes and plasma cells. In the bone marrow, in the splenic pulp and especially in

the renal infiltrations there were many foci of erythropoiesis composed of erythroblasts and large orthochromatic normoblasts. The bone marrow and the splenic pulp also contained small groups of neutrophilic myelocytes and mature leukocytes. In the bone marrow and in the renal infiltrations, single well preserved megakaryocytes were present.

In striking contrast to the scarcity of the granulocytes in the other organs, the alveolar exudate in the pneumonic areas was composed chiefly of mature polymorphonuclear leukocytes, which were embedded with a fine net of fibrin and were mixed with a few macrophages and erythrocytes (fig. 1). The lumen of the small

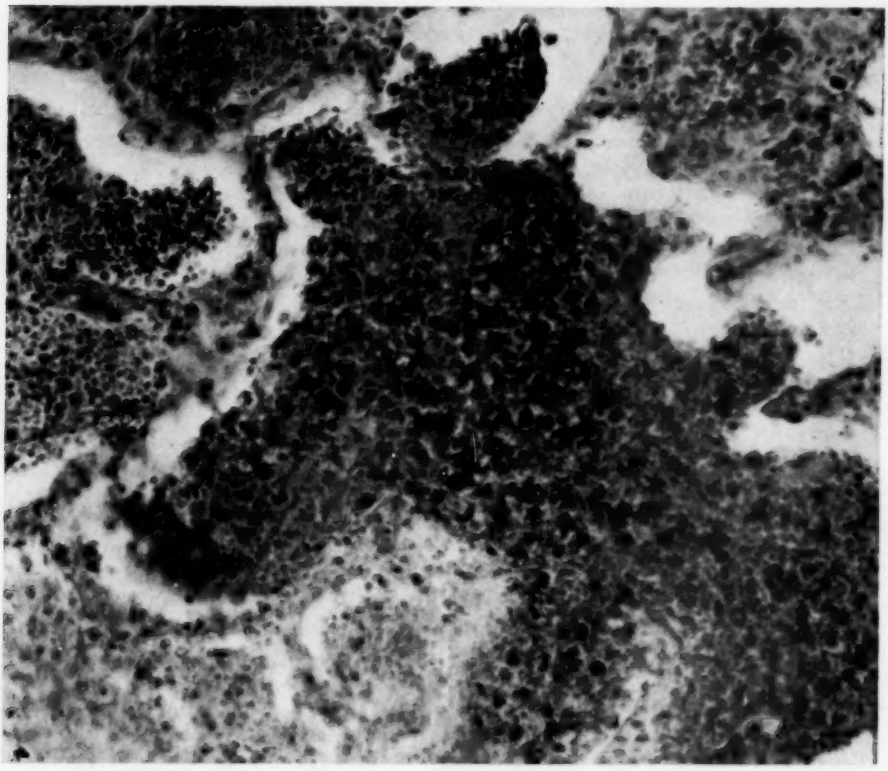

Fig. 1 (case 1).—Pneumonic area. The exudate is chiefly composed of granulocytes; oxydase reaction; × 150.

bronchi and bronchioli was occluded by plugs of fibrin. The alveolar capillaries contained single granulocytes and a moderate number of lymphoid cells.

CASE 2.—*Serofibrinous Peritonitis Following a Splenic Infarct in a Case of Chronic Lymphatic Leukemia.*—A white man, aged 57, was admitted to the hospital stating that he had lost 50 pounds (22.7 Kg.) in weight during the last eight months. He also had noted an enlargement of the lymph nodes and complained of severe pains in the arches of his feet. Shortly prior to his admission he had a severe attack of sore throat. On admission, the temperature was 98 F.; the pulse rate was 120, and the respiratory rate, 24. The blood pressure was 158 systolic and 87 diastolic. The anterior and posterior cervical lymph nodes and

the submandibular, inguinal and axillary nodes were pea-sized, soft, discrete and painless. The lower pole of the spleen could be palpated 5 fingerbreadths below the costal arch, and the lower border of the liver was felt 2½ fingerbreadths below the costal arch.

The erythrocyte count was 3,250,000; the hemoglobin content (Dare) was 60 per cent. The white blood cell count was 139,000, with lymphocytes (about one and one-half the size of normal lymphocytes with coarsely trabeculated nuclei and narrow rims of deeply basophilic cytoplasm) 98 per cent and lymphoblasts (three times the size of lymphocytes) 2 per cent. Under treatment with benzene, the lymph nodes and the spleen became smaller, and the white count dropped to 98,000. The lymphocytes diminished to 95.5 per cent, and 2.5 per cent neutrophils were counted.

In the fifth week of the patient's stay in the hospital, he suddenly began to have a severe pain in the region of the spleen, and the temperature rose to 102 F. Two days prior to this attack he had a sore throat. He became rapidly weaker and died four days after the onset of the abdominal pain.

Autopsy: Post mortem, diffuse serofibrinous peritonitis with 400 cc. of free exudate was found. The exudate contained many typical pus cells and very few lymphoid cells, and on being cultured yielded a hemolytic streptococcus. The spleen weighed 1,810 Gm. and was covered by a thick, soft, fibrinous membrane; in the lower third of the posterior margin there was a recent light purple-gray, sharply demarcated anemic infarct. The liver measured 30 by 20 by 10 cm., was soft and pale brown, and contained single pinhead-sized whitish nodules. All the lymph nodes were enlarged, and the largest nodes, which measured 40 by 35 by 15 mm., were found along the extrahepatic bile ducts, the aorta and the iliac vessels. The bone marrow was moderately firm and purplish pink mottled with darker purple-red. Cholelithiasis was present. There was septic staining of the intima of the aorta.

Histologic Observations: Microscopically, the bone marrow was made up chiefly of oxydase-negative lymphoid cells, the majority of which were slightly larger than a lymphocyte. The nuclei contained coarse chromatin granules. There were single large, deeply basophilic round cells and a few plasma cells. Around the blood vessels, numerous nests of young neutrophilic and oxyphilic myelocytes were found. The origin of these cells could be traced to the reticular adventitial cells. There were no relations between the granulated elements and the lymphoid cells. In addition to the granulopoietic areas, there were small foci of erythropoiesis and many young and mature megakaryocytes. The spleen showed an enormous predominance of the lymphoid cells and very few other elements, namely, free histiocytes, neutrophilic and oxyphilic myelocytes and an occasional plasma cell. The infarcted area, however, was surrounded by a zone of oxydase-positive cells with bean-shaped and lobulated nuclei. The larger veins leading to the infarct were occluded by thrombi composed of fibrin and lymphoid cells. Gram stain revealed in the infarct numerous streptococci.

The structure of the lymph nodes was obscured by a diffuse accumulation of the lymphoid cells described in the bone marrow. In the peribiliary, peripancreatic and splenic hilus lymph nodes there were many neutrophilic myelocytes and leukocytes and a few oxyphilic granulocytes. They were present in the distended sinuses as well as between the lymphoid cells. The sinuses also contained many streptococci. In the liver, the periportal tissue and the walls of the sublobular veins were densely infiltrated by the lymphoid cells, which also filled the portal capillaries. In the periphery of the periportal infiltrations and in some of the portal capillaries, large round cells were found, the cytoplasm of which contained

fine, purple-pink granulation. A few of these cells had coarse, oxyphilic granulation. Where the granulated elements filled the portal capillaries, the adjacent Kupffer cells contained similar granulation. The kidneys showed focal perivascular accumulations of lymphoid cells, and these cells also filled the tufts of the glomeruli. The lymphatic tissue of the pharynx and intestine was unchanged.

CASE 3.—*Streptococcic Septicemia Complicating Subacute Lymphatic Leukemia.*—A Filipino, 19 years of age, on admission to the hospital on Nov. 26, 1929, reported that he had had his tonsils removed one month before, and that a week later his neck increased in size, first on the right side and then on the left side, and that this swelling caused him difficulties in swallowing and breathing. The temperature was 98.6 F.; the pulse rate was 60, and the respiratory rate, 20. External examination revealed a generalized lymphadenopathy, most marked in the neck. The glands ranged in size up to that of a walnut, and were matted together but not adherent to the skin. The result of the Kahn test was negative. The x-ray picture of the chest was negative.

The erythrocyte count was 3,800,000; the hemoglobin content (Dare) was 55 per cent. The white blood cell count was 10,000, with neutrophils 70, lymphocytes 25 and monocytes 5 per cent.

Biopsy of a cervical lymph node showed lymphatic leukemia. The clinical diagnosis was: aleukemic lymphadenosis. Under treatment with the x-rays, the patient's condition improved markedly, and he returned home on Dec. 21, 1929. He was readmitted to the hospital on Feb. 17, 1930, acutely ill, feeling very weak with dull aching pains over the entire body. He felt hot and had nosebleed about once a day, losing a teaspoonful of blood. He complained further of severe frontal headache, accompanied by dizziness and spots before the eyes, and a constant cough productive of dark red blood. His temperature was 103.4 F.; his pulse rate was 110.

The lymph nodes were distinctly larger than on his first admission. There were petechial spots over both eyelids and on the hard palate. The gums were swollen and bluish, and there was marked mediastinal dulness. A systolic murmur with a systolic thrill was heard over the entire precordium. The spleen and liver were not palpable.

The erythrocyte count was 1,500,000; the hemoglobin content, 40 per cent. The white blood cell count was 53,000, with lymphoblasts 79, lymphocytes 16 and neutrophils 16 per cent. There were slight anisocytosis and poikilocytosis, with 2 nucleated red cells per hundred white cells. While the patient was in the ward, the nosebleeds became more and more severe, and the temperature remained around 103 F. One day before death, the erythrocyte count was 980,000; the hemoglobin content, 15 per cent. The white count was 850 (!), with lymphoblasts 78 and lymphocytes 22 per cent. On Feb. 25, 1930, the patient died.

Autopsy: At autopsy, the peripheral, thoracic and abdominal lymph nodes were uniformly enlarged, reaching a diameter of 50 by 20 by 25 mm. They were soft and spongy and varied in color from deep purple-gray to reddish gray. The bone marrow was semiliquid and purple-gray. The thymus weighed 26 Gm. and was light pinkish gray. The spleen weighed 170 Gm. It was very soft and dark purple-gray with small light gray follicles. The liver weighed 1,430 Gm. Other changes were: severe fatty degeneration of the myocardium and liver, anemia of the kidneys, gangrenous stomatitis and petechial hemorrhages underneath the epicardium and endocardium and in the gastric mucosa and renal pelvis.

Histologic Observations: Microscopically, the lymph nodes appeared very loose, and the normal structure was completely obscured. The sinuses and capillary blood vessels were much dilated, and the reticulum was very prominent

because of disintegration of the lymphatic cells. The majority of these cells, which were slightly larger than lymphocytes, had nuclei the chromatin of which had been separated into coarse granules and the membrane of which had disappeared. Single large round cells with pale nuclei and ample, basophilic cytoplasm had escaped the nuclear disintegration. The cytoplasm of these cells contained fine, oxydase-positive granulation. In the abdominal lymph nodes, the granulated cells were more numerous than in the other lymph nodes, and there were also small nests of erythroblasts and normoblasts and single megakaryocytes. In the spleen, the breaking up of the nuclei of the lymphoid cells was even more striking than in the lymph nodes, and in many places only the reticular cells of the cords and the lining cells of the sinuses were left. In the follicles, too, the lymphoid cells were severely affected. The periportal tissue of the liver contained numerous lymphoid cells, which were found also about the sublobular veins and in the portal capillaries. In the latter location, they formed small groups. The karyorrhexis of the nuclei was less marked than in the lymph nodes and spleen. About 94 per cent of the cells of the bone marrow were lymphocytes with narrow rims of cytoplasm and nuclei showing a coarse chromatin net. The majority of the cells were well preserved, and only a few larger lymphoid cells revealed the nuclear changes previously described. There were 3.8 per cent plasma cells, 3.8 per cent normoblasts and 0.8 per cent oxyphilic granulocytes. About the vessels at the corticomedullary border of the kidney, accumulations of lymphoid cells were found. These cells also dominated in the thymus, and Hassall's bodies were scanty. Gram stain demonstrated in the lymph nodes, spleen and bone marrow long chains of streptococci. Pieces taken from the swollen gums showed deep necrosis with an enormous number of cocci, fusiform bacilli and spirochetes. Underneath the necrosis there were extravasations of blood and a few loosely scattered lymphoid cells. No granulocytes could be detected. The picture was similar to that seen in agranulocytosis or panmyelophthisis. Cultures of the cardiac blood demonstrated hemolytic streptococci.

### MYELOGENOUS LEUKEMIA

CASE 4.—*Suppurative Prostatitis in a Case of Acute Promyelocytic Leukemia.*—The clinical data of this case are incomplete. A white man, aged 34, complained of general malaise, headache and chilly feeling. The axillary and inguinal lymph nodes were cherry-sized. The lower pole of the spleen was at the costal arch. Petechial hemorrhages were found over the neck, shoulders and thighs. The duration of the illness was thirty days. The result of the Wassermann and Kahn tests was four plus.

The erythrocyte count was 1,020,000; the hemoglobin content (Dare), 32 per cent. The white blood cell count was 6,100, with myeloblasts 15, promyelocytes 31, neutrophilic myelocytes 6, neutrophils 18, eosinophilic myelocytes 3, eosinophilic leukocytes 1, lymphocytes 24 and monocytes 2 per cent. Marked anisocytosis and poikilocytosis were present, with 1 normoblast per hundred white cells. There were 15 per cent reticulated erythrocytes.

Autopsy: Post mortem there was shown moderate enlargement of the spleen (390 Gm.) and of the liver (2,065 Gm.), eccentric hypertrophy of the heart (410 Gm.) with small hemorrhages in the papillary muscles of the left ventricle, enlargement of the peripancreatic, peribiliary and axillary lymph nodes, marked generalized anemia and petechiae in the skin and epicardium. The prostate measured 6 by 3.25 by 2.5 cm. and was firm. In the left lobe there was a cavity 2 cm. in diameter, which was filled by thick, greenish pus. In the right lobe, a similar but smaller cavity was found.

Histologic Observations: The bone marrow showed a predominance of young neutrophilic myelocytes with many mitoses (44.8 per cent). There were many small groups of myeloblasts and oxyphilic myelocytes and very few nucleated red cells and megakaryocytes. There were 14.2 per cent lymphocytes and 4.5 per cent plasma cells. The abdominal lymph nodes revealed advanced myeloid metaplasia, chiefly neutrophilic promyelocytes. In the axillary and inguinal nodes, the myeloid transformation was less marked. The splenic pulp contained an enormous number of large round cells with round, light nuclei and fine, purple-pink granulation. There were a few myeloblasts, normoblasts and oxyphilic granulocytes. The follicles were small and lymphocytic. In the liver, the periportal tissue and the portal capillaries were filled by young, oxydase-positive cells of promyelocyte type. Small foci of granulopoiesis were present in the myocardium about the hemorrhages, in the stroma of the kidney and pancreas, in the medulla of the suprarenal gland, in the mucosa of the colon and about the blood vessels of the lung.

The stroma of the prostate was infiltrated by oxydase-positive cells with round, bean-shaped and lobulated nuclei. Similar cells were found in the lumen of some of the glands. There were areas of diffuse suppuration. The differential count of these areas was: mature neutrophilic leukocytes, 94.5 per cent, and myelocytes, 5.5 per cent. The differential count of the infiltrations was: neutrophilic leukocytes, 52.5 per cent; myelocytes, 20.5 per cent; eosinophilic leukocytes, 20.5 per cent; lymphocytes, 20.5 per cent, and plasma cells, 1 per cent. No microorganisms could be found in the abscesses.

Case 5.—*Diphtheritic Colitis in a Case of Chronic Myelogenous Leukemia with Terminal Acute Exacerbation.*—An Italian, 38 years of age, was well until April, 1930, when he was bothered by an intermittent pain in the left sacro-iliac region and by great fatigability. In June, he noticed a mass in the left hypochondrium. His condition was diagnosed as myelogenous leukemia, and roentgen treatment was applied over a period of four months. In all, twenty-five treatments were given over various areas, one-third erythema dose each. The white count, which on admission was 103,500, fell to 26,000 and then rose again to 60,000 to remain stationary. The last treatment was given on October 30, and the patient went home. Soon after this last treatment, he started to have a slight intermittent fever. The temperature went up to 100.2 F. He grew gradually weaker. The red count now was 4,500,000, but dropped within the next two weeks to 1,500,000, while the hemoglobin diminished from 70 to 45 per cent. A white count done two days prior to death revealed 41,950 cells, of which 81 per cent were myeloblasts, 3 per cent promyelocytes, 3 per cent myelocytes, 12 per cent neutrophils, 2 per cent basophils and 1 per cent lymphocytes. There was 1 normoblast to 200 white cells.

Anatomic Diagnosis: The anatomic diagnosis was hyperplasia of the cervical, axillary, inguinal, tracheobronchial, peri-aortic, peribiliary and peripancreatic lymph nodes; a huge splenic tumor (1,660 Gm.); moderate enlargement of the liver (2,230 Gm.); petechial hemorrhages in the mucosa of the lips, skin, epicardium, endocardium, pleura and lungs, and diphtheritic colitis. The mucosa of the transverse colon was raised to form soft, reddish-gray plaques, 5 mm. in diameter. Near the splenic flexure and extending through the descending and sigmoid colon into the rectum the mucosa was transformed into a 3 mm. thick, dirty gray, adherent membrane.

Histologic Observations: The bone marrow was myeloblastic. Scattered between the large, round, oxydase-positive cells, which were often found in the stage of mitotic division, were a few neutrophilic myelocytes, large orthochromatic normoblasts and very few intact megakaryocytes. The lymph nodes showed a similar picture, and in the liver the portal capillaries and the portobiliary septums

contained a great many myeloblasts and a few neutrophilic myelocytes. In the splenic pulp, however, there were decidedly more neutrophilic myelocytes, and there were also many nucleated red cells. In the inflamed colon, polymorphonuclear leukocytes were so numerous that one would not think that the sections came from a case of myeloblastic leukemia (fig. 2). They formed dense accumulations underneath the membrane of necrotic tissue. Myeloblasts and myelocytes were absent, and it was only in the edematous submucosa that a few of these cells could be detected.

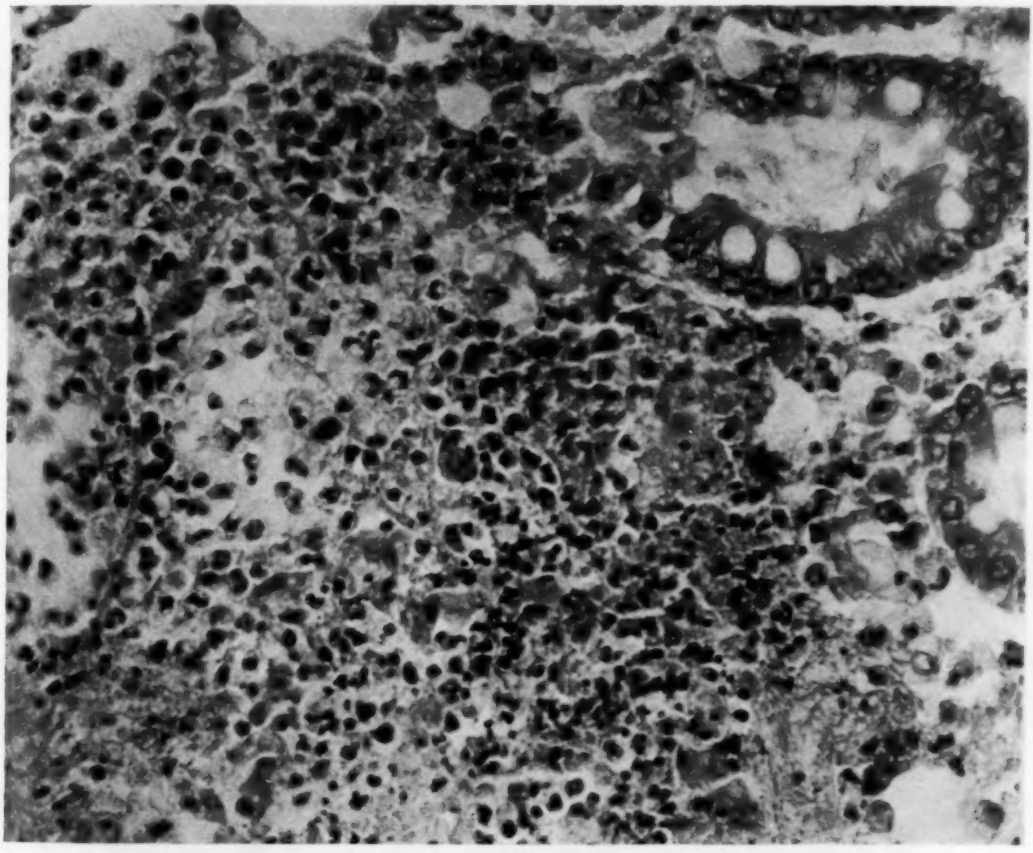

Fig. 2 (case 5).—Diphtheritic colitis. Note the accumulation of mature leukocytes underneath the necrotic membrane; × 600.

CASE 6.—*Diphtheritic Tonsillitis and Laryngitis and Confluent Bronchopneumonia in a Case of Acute Stem Cell Leukemia.*—A white man, aged 35, stated that about six weeks before admission to the hospital he caught a severe cold which he tried to abort by sweating. Ever since, cough and profuse expectoration had persisted. Five days before admission, severe pains in the chest developed. During the last two weeks his temperature often went up to 103 F. The physical findings consisted of enlargement of the tonsils, pharyngitis with much mucopurulent secretion, a rough pleural rub over the base of the right lung and a pulse rate

of 110. The temperature on admission was 102 F. The patient died three days after entrance.

The erythrocyte count was 2,340,000; the hemoglobin content was 50 per cent. The white blood cell count was 19,300. Stem cells (cells with an ample, light blue cytoplasm, which is often vacuolated and is free from oxydase granules, and round nuclei, sometimes indented, containing a fine chromatin net and two or three large nucleoli) numbered 95 per cent; promyelocytes, 1 per cent; neutrophilic leukocytes, 1 per cent, and lymphocytes, 3 per cent. One nucleated red cell per hundred white cells was found. Anisocytosis and poikilocytosis were present.

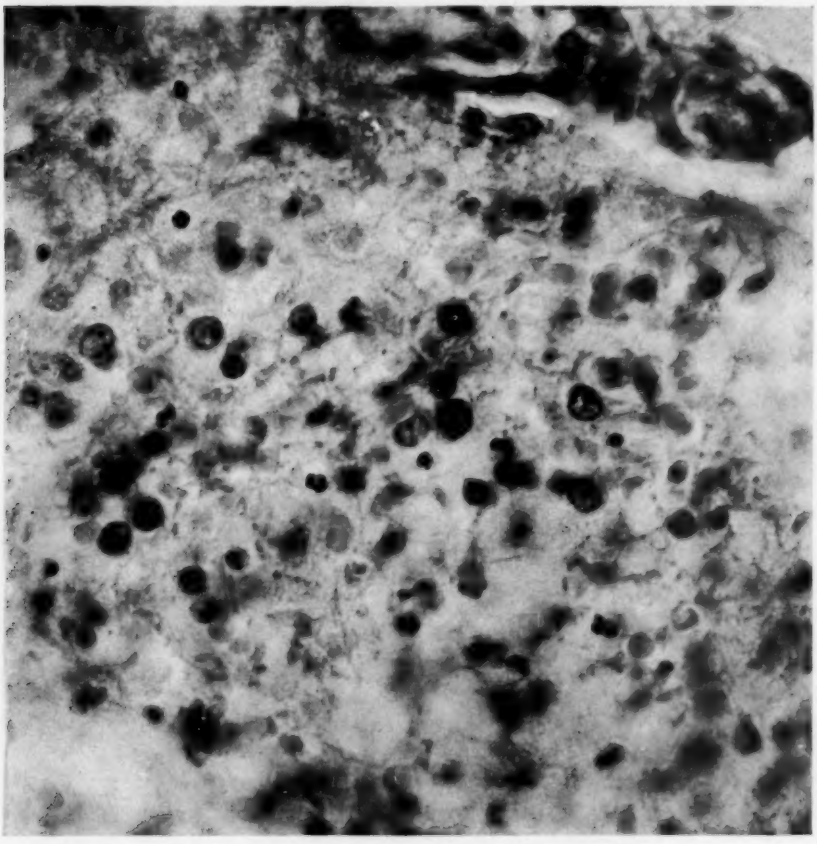

Fig. 3 (case 6).—Pneumonic area. The exudate contains single stem cells and a few small and degenerated leukocytes; × 600.

Anatomic Diagnosis: The anatomic diagnosis was petechial hemorrhages in the skin, epicardium, pleura, renal pelvis and colon mucosa; slight enlargement of the spleen (205 Gm.); moderate enlargement of the liver (2,360 Gm.); enlargement of the suprarenal glands (24 Gm.); enlargement of the lymph nodes up to 30 mm. in greatest diameter (the nodes were soft and light purple-gray with darker red areas); diphtheritic tonsillitis and laryngitis; edema of the epiglottis; confluent bronchopneumonia in both lungs, especially the right; severe anemia and hydremia; herpes of the left ear.

Histologic Observations: The bone marrow was very cellular and was composed mainly of large round cells with pale round nuclei and narrow rims of homogeneous, basophilic cytoplasm. The nuclei contained two or three distinct basophilic nucleoli. Many cells had two nuclei. Mitoses were numerous. The oxydase reaction was negative. There was an occasional cell with purple-pink granulation and a round nucleus. There was a single smaller cell with coarse oxyphilic granulation. A few polychromatophilic normoblasts, plasma cells and mast cells completed the picture. In some places there were small, sharply separated lymph follicles composed of small lymphocytes.

The cells described in the bone marrow predominated also in the liver and in the spleen, while in the lymph nodes they were less numerous and were mixed with small lymphocytes and plasma cells. The medulla in the suprarenal glands was densely infiltrated by the indifferent round cells, which also filled the capillaries of the reticular zone of the cortex.

The tonsils consisted of lymphadenoid tissue, and there were no abnormal elements. The surface was diffusely necrotic, and the necrosis extended in places deep into the tissue. It contained an enormous number of streptococci, and underneath it there were no reactive changes, and oxydase-positive cells were completely absent. The larynx showed a similar picture, and here, too, the complete lack of reaction about the necrosis was striking. The capillaries and small veins were occluded by plugs of fibrin. In the areas of consolidation of the lung, the alveoli were filled by an exudate that consisted chiefly of fibrin threads. In some of the alveoli, the fibrin was scanty, and in its meshes were found a few large round cells with one or two pale nuclei and narrow rims of basophilic, oxydase-negative cytoplasm. Here and there a small neutrophilic leukocyte with a shrunken and broken up nucleus and poorly defined oxydase-positive granulation was visible (fig. 3). The alveolar exudate contained many streptococci. From the cardiac blood a pure culture of hemolytic streptococci was obtained.

Case 7.—*Hemorrhagic Fibrinous Pericarditis in a Case of Acute Myelogenous Leukemia.*—A colored woman, aged 53, complained that during the last year she had lost 60 pounds (27.2 Kg.), and that she had been suffering from progressive weakness. Since three weeks before admission she felt an aching and stitching epigastric pain, radiating to the back. She vomited from two to four times a day one-half cup of bright red clotted blood, and her stools were dark red or black. She had a history of malaria, an infra-umbilical laparotomy, two miscarriages and six normal deliveries.

The temperature was 97.2 F.; the pulse rate was 118, and the respiratory rate, 36. The blood pressure was 118 systolic and 80 diastolic. The eyes were fixed. There was slight cervical lymphadenopathy. The lungs showed decreased expansion on the left side; there were suppressed breath sounds and an absence of tactile fremitus in the left lower axillary region. A systolic murmur was heard over the apex of the heart. The liver extended four fingerbreadths below the costal arch. In the left hypochondrium, a firm mass was felt, which was believed to be the spleen. There was tenderness on deep palpation over the upper part of the abdomen. The patellar reflexes were absent.

The erythrocyte count was 2,400,000; the hemoglobin content was 70 per cent. The white blood cell count was 90,000, with myeloblasts 5.2, promyelocytes 44, myelocytes 5.2, neutrophils, 41.6, eosinophils 0.4, basophils 1.6 and lymphocytes 2 per cent. There were 8 normoblasts per hundred white cells.

The patient died three days after admission.

Autopsy: The spleen showed marked enlargement (440 Gm.). It was soft, and the pulp was light purple-red without structural markings. The liver showed

moderate enlargement (2,225 Gm.). There was swelling of the peripancreatic, peri-aortic and peribiliary lymph nodes. The largest nodes measured 5 cm. in diameter. The marrow of the femur was reddish gray and moderately firm. There were syphilitic aortitis with insufficiency of the aortic valve, eccentric hypertrophy of the heart (450 Gm.), verrucous endocarditis of the mitral valve, and hemorrhagic-fibrinous pericarditis. The pericardial sac contained 300 cc. of a cloudy, blood-stained fluid. The surface of the heart was covered by a soft, loosely adherent, light pink-gray membrane with distinct villi. The enlarged pericardial sac caused compression of the left lower pulmonary lobe. There was superficial necrosis of Peyer's patches of the lower ileum. A nodose goiter was present.

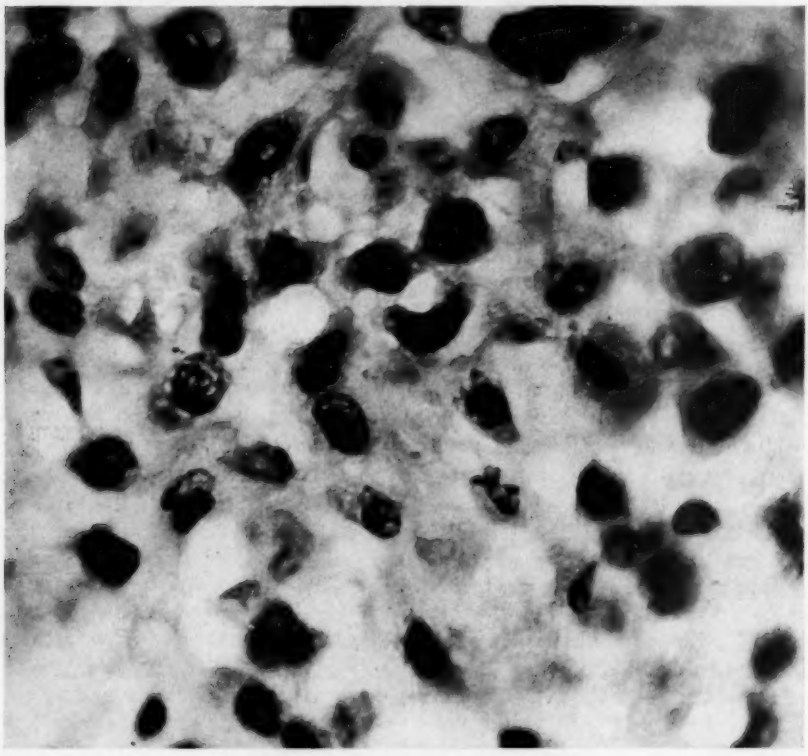

Fig. 4 (case 7).—Cytoplasmic syncytium in the epicardium; beginning condensation of the cytoplasm about the nuclei; × 1,200.

Histologic Observations: The bone marrow was very cellular and showed active granulopoiesis with 43 per cent myelocytes and 9.8 per cent mature neutrophilic leukocytes. There were only few oxyphilic myelocytes and leukocytes, but many foci of erythropoiesis composed of erythrogonia, erythroblasts and normoblasts. In addition to these cells, there were 5 per cent plasma cells, 0.8 per cent monocytoid elements and 0.6 per cent megakaryocytes. The splenic pulp was exceedingly cellular, the sinuses were hardly discernible, and the follicles were reduced to small perivascular accumulations of lymphocytes. Neutrophilic myelocytes were by far predominating. Scattered between them were small groups of myeloblasts, many orthochromatic normoblasts, few oxyphilic granulocytes and plasma cells.

The portal capillaries were stuffed by young neutrophilic myelocytes. There were also small groups of myeloblasts and orthochromatic normoblasts. The periportal tissue was infiltrated by myelocytes, lymphocytes and plasma cells. The abdominal lymph nodes contained numerous neutrophilic myelocytes, few oxyphilic myelocytes and single young and mature megakaryocytes. In the medullae of the kidneys were foci of granulopoiesis, which were much richer in oxyphilic myelocytes than were the granulopoietic foci in the other organs. The ulcerated plaques of the ileum showed many neutrophilic myelocytes and relatively few lymphatic elements. Underneath a superficial layer of necrosis, a narrow layer of mature neutrophils was found.

The cusps of the mitral valve revealed subendothelial circumscribed accumulations of mononuclear cells with oval or lobulated nuclei and ample, basophilic

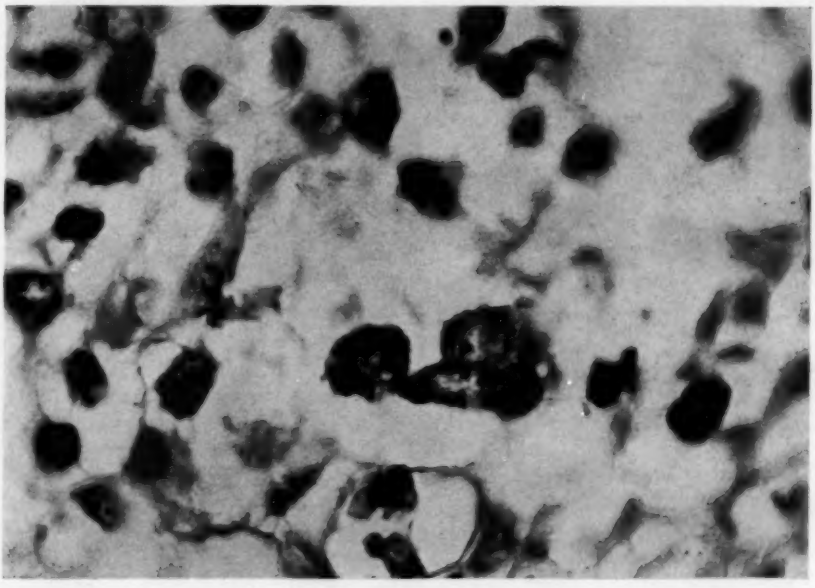

Fig. 5 (case 7).—Cytoplasmic syncytium in the epicardium. Three cells of myeloblast type are seen entering a pore; × 1,200.

cytoplasm. In the thickened marginal portions, nodular areas stood out, which were composed of branched and stellate cells. These areas possessed a distinct affinity to the basic stains. Where the nodules protruded over the surface, they were covered by a homogeneous, hyaline material without bacteria.

The histologic observations in the inflamed epicardium were so unusual that they deserve a detailed description. The surface of the epicardium was covered by a layer of fibrin, which was thrown up to short and anastomosing villi. Between the villi there were a few ill-defined and degenerated granulocytes. Underneath the fibrin was a layer of cellular granulation tissue, which was very different from that commonly found in fibrinous inflammation with organization. It appeared as a spongy, protoplasmic syncytium with small, round, empty spaces. This syncytium contained round or oval nuclei with a distinct chromatin net, and the cytoplasm, which stained pale blue after Giemsa, was more compact about the nuclei (fig. 4).

From this indifferent, mesenchymatous syncytium two strains of cells developed. First, the cytoplasm around the nuclei became deeply basophilic, the chromatin content of the nuclei decreased, and one or two nucleoli become visible. Between the deeply basophilic cytoplasm and the rest of the syncytium a narrow crevice was formed, and the cell lost its connection with the protoplasmic net to enter one of the round, empty spaces previously described (fig. 5). The cytoplasm then contained fine, purple-gray granulation. The second strain of cells was characterized by progressing condensation of the chromatin until the nuclear structure was completely obscured. At the same time, the cytoplasm, which at first was deeply

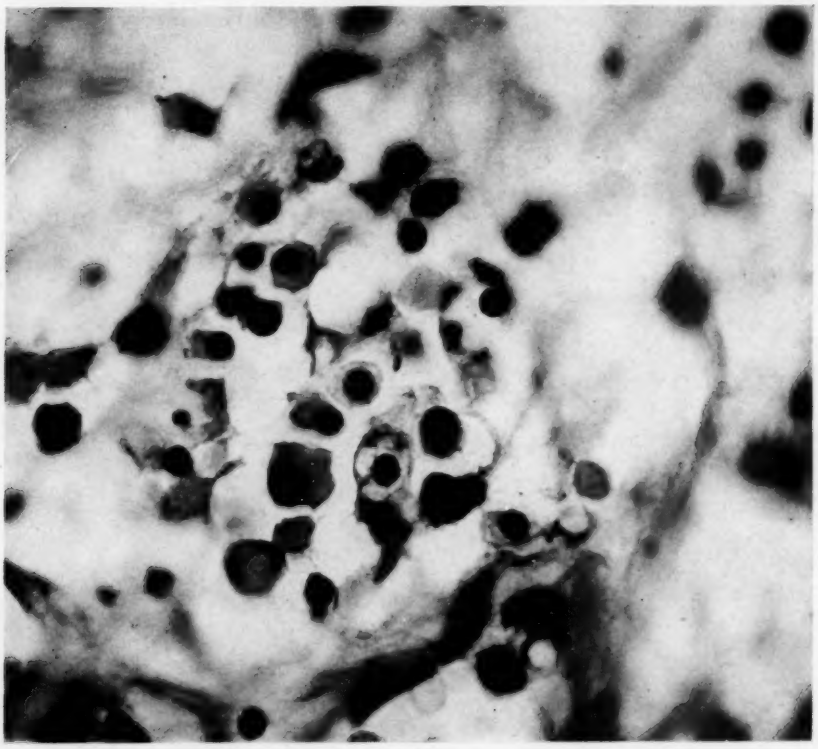

Fig. 6 (case 7).—Cytoplasmic syncytium in the epicardium; a group of nucleated red cells in a pore of the syncytium; × 1,200.

basophilic, assumed a purple-red color which gradually changed to a bright brick red. Here and there one saw bright brick red droplets around the nucleus (fig. 6). These cells, which varied in size, also were discharged into the empty spaces. Where the protoplasmic syncytium approached the myocardium, the picture was somewhat different. The cytoplasm seemed to produce fine, parallel fibrils, which gradually filled the empty spaces. There was a moderate number of wide capillary blood vessels lined by flat endothelium and containing many nucleated cells, which did not show any relations to the endothelium. The myocardium was free from interstitial infiltrations. The histologic picture of the syphilitic aortitis was not different from that commonly found. There was much scarring of the media.

CASE 8.—*Bilateral Pyelitis and Pyelonephritis and Recent Fibrinous Pericarditis in a Case of Chronic Myelogenous Leukemia.*—A white man, 48 years of age, an iron molder, felt well until five and a half years ago when he noticed languor and tired feeling after work. At times he was exhausted to the point that he was unable to move for from three to four hours. Shortly afterward headaches and head noises appeared that were relieved only by sleep. Six months later he discovered an enlargement of the left side of the abdomen. A physician was consulted, who prescribed irradiation of the spleen. After this treatment, all the symptoms subsided, and the patient was able to return to work. With roentgen treatment given every three months the patient did fairly well, but later the symptoms reappeared, and he went to the hospital.

On physical examination, the spleen was found extending down to the umbilicus, and the liver was palpable and very firm. The erythrocyte count was 2,560,000; the hemoglobin content was 60 per cent. The white cell count was 185,000, with a predominance of myelocytes. Treatment with the x-rays was again instituted, and the white count went down to 94,000, but soon returned to 192,000. The patient went home for a week and returned with marked weakness and severe pains in the abdomen. The erythrocyte count was 1,820,000, with hemoglobin 40 per cent. The white cell count was 31,000, with myeloblasts 24, promyelocytes 9.4, myelocytes 27, neutrophils 32.6, eosinophilic myelocytes 1.4, eosinophilic leukocytes 0.4, basophils 1.2 and lymphocytes 0.4 per cent. One day before the patient died, a definite pericarditic rub was heard. There was no rise in the temperature, and the patient expired quietly after an illness of five and a half years.

Anatomic Diagnosis: The anatomic diagnosis was as follows, large tumor of the spleen (1,050 Gm.); marked enlargement of the liver (3,460 Gm.); slight swelling of the peripancreatic, mesenteric, peri-aortic, inguinal and cervical lymph nodes; light yellow-green medullary bone marrow; eccentric hypertrophy of the heart (450 Gm.); fatty degeneration of the myocardium; recent fibrinous pericarditis; bilateral pyelitis; abscesses in the medulla in both kidneys (both renal pelves contained several light yellow, mulberry-shaped concretions up to 2 mm. in diameter); bilateral hydrothorax; hydropericardium, and ascites.

Histologic Observations: The bone marrow was very cellular and contained numerous myeloblasts, promyelocytes, neutrophilic and oxyphilic leukocytes and megakaryoblasts. The latter resembled overgrown myeloblasts. Eosinophilic myelocytes were relatively scanty. Erythropoiesis appeared in small foci of erythrogonia, erythroblasts and normoblasts. About 1 per cent of the cells was a mature megakaryocyte. The hepatic cells of the acinar centers were necrotic, while the Kupffer cells were filled by iron granules. Around the necrotic areas, much fat had accumulated in the hepatic cells. The portal capillaries contained a great many nucleated cells, chiefly neutrophilic myelocytes, then myeloblasts, oxyphilic granulocytes, normoblasts and few erythroblasts and erythrogonias. The periportal septums showed only a few loosely scattered myelocytes, myeloblasts and eosinophils.

In spite of the great cellularity of the splenic pulp, the reticulum was very prominent. The pulp was composed of an enormous number of oxydase-positive cells, among which promyelocytes and myeloblasts predominated. There were also many oxyphilic myelocytes and leukocytes and normoblasts, the latter varying considerably in size. Mature neutrophils were scanty. Here and there a young or fully developed megakaryocyte was found. The follicles had disappeared. The reticular cells were filled by iron pigment. The abdominal lymph nodes contained a varying number of myeloid cells. In the peribiliary nodes, the myeloid tissue was restricted to the interfollicular areas, and the follicles were still visible. In

the peri-aortic lymph nodes, the lymphatic tissue had been completely substituted by granulopoietic tissue. The inguinal lymph nodes were rich in young and adult megakaryocytes.

The abscesses in the medulla of the kidney showed diffuse coagulation necrosis with clumps of degenerated polymorphonuclear leukocytes and nuclear débris. There was no well defined zone of demarcation save for a narrow rim of leukocytes and small round cells. The wall of the pelvis was densely infiltrated by various types of immature blood cells, most of which were oxydase-positive. Some of the oxydase-positive cells were large, distinctly larger than in the other organs. Their shape was irregular, and blunt processes projected from the surface. The nuclei were round and pale with fine chromatin granules. A few of the oxydase-positive cells were flat and drawn out. The fibrocytes between the infiltrating cells were very large; their cytoplasm stained basophilic and was finely vacuolated. The

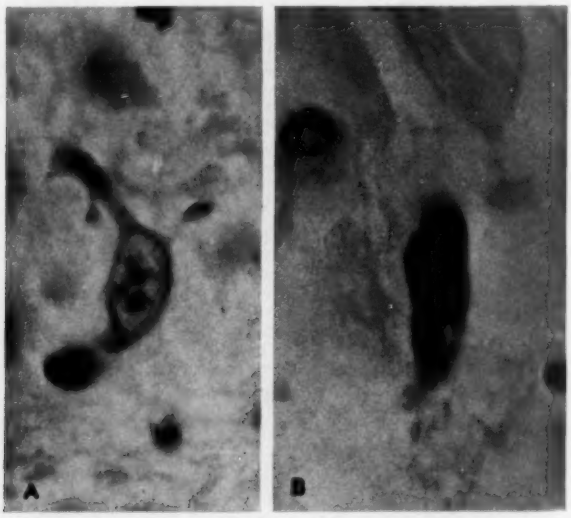

Fig. 7 (case 8).—*A* shows a large fibrocyte in the epicardium. Note the deep basophilic coloration of the cytoplasm. The large pale nucleus with the distinct nucleoli resembles the nucleus of a hemocytoblast; × 1,200. *B* shows the fibroblast after it has become separated. The cytoplasm contains a fine, oxydase-positive granulation, which is not visible in the halftone picture; × 1,200.

nuclei were pale and contained prominent nucleoli. Between these cells there were single megakaryocytes and oxyphilic myelocytes.

The pericarditis was more recent than in case 7. The fibrin that covered the surface formed slender trabeculae, and near the base desquamated mesothelial cells could be seen. Only a few immature white blood cells were present. The epicardium was loosened, and the fibrocytes were very prominent as large, branched elements with a basophilic, often finely vacuolated cytoplasm and round nuclei containing either a single angular or several round nucleoli (fig. 7 *A*). The loosened connective tissue with the large fibrocytes formed a net in the meshes of which accumulations of promyelocytes, oxyphilic and neutrophilic myelocytes and single lymphocytes and plasma cells were found. Neutrophilic leukocytes, too, were present, most of which had deeply lobulated nuclei and very indistinct granulation.

There were also the large cells with the blunt protoplasmic projections described in the renal pelvis (fig. 7 *B*). In the Giemsa sections, the cytoplasm assumed a bluish-gray color, and very fine, purple-pink granules could be differentiated. The nuclei were round or oval and contained fine chromatin granules and two or three distinct nucleoli. The capillaries of the epicardium were dilated and contained a varying number of immature blood cells. Though the endothelium was swollen, it remained pale and did not reveal an increased affinity to the basic stain. About the capillaries there were large branched cells, which seemed to be connected with the swollen fibrocytes.

CASE 9.—*Chronic Pneumonia in a Case of Chronic Myelogenous Leukemia.*—A white man, aged 80, was under the care of an outside doctor and was in the hospital for only four and a half hours. Six years before admission he had been operated on for ulcers of the stomach, and five years before admission he had a gas anesthesia for extraction of teeth from which he was resuscitated with great difficulty. One and a half years before admission he began to bleed from the mouth and the rectum, and a small cut on the finger would bleed for a day or two.

The temperature was 94.2 F.; the respiratory rate, 24; the pulse rate, 60. The heart was enlarged, and the tones were very weak. The liver and the spleen were markedly enlarged. The urine contained two plus albumin and many hyaline and granular casts.

The erythrocyte count was 2,040,000, with a hemoglobin content of 20 per cent. The white cell count was 320,000, with myeloblasts 1, promyelocytes 7, metamyelocytes 4.5, neutrophils 67.5, eosinophils 2.5, basophils 8 and lymphocytes 9.5 per cent. There were 14 normoblasts per hundred white cells, also marked anisocytosis and hypochromia.

Anatomic Diagnosis: The anatomic diagnosis was marked enlargement of the spleen (530 Gm.) and liver (1,980 Gm.); enlargement of the peri-aortic lymph nodes up to a diameter of 18 mm.; dark red bone marrow; hypertrophy of the heart (525 Gm.); old gastrojejunostomy with two ulcers in the jejunum opposite the opening; healed peptic ulcer of the stomach with marked pyloric stenosis; chronic emphysema of the lungs and chronic pneumonia in the upper half of the right upper lobe, and arteriosclerotic contraction of the kidneys.

Histologic Observations: Microscopic examination of the bone marrow revealed great cellularity with numerous promyelocytes and neutrophilic and oxyphilic myelocytes and groups of myeloblasts. There were many areas of erythropoiesis and many megakaryocytes. The cords of the splenic pulp contained many myeloblasts, promyelocytes and a moderate number of neutrophilic and oxyphilic granulocytes. The abdominal lymph nodes showed moderate myeloid metaplasia with a predominance of young neutrophilic myelocytes. In contrast to the spleen and the abdominal lymph nodes, the liver showed only a few small intracapillary granulopoietic foci. The centers of the acini were necrotic. The histologic picture of the jejunal ulcers was that of chronic peptic ulcers with broad zones of fibrinoid necrosis passing into a moderately cellular granulation tissue containing a few neutrophilic myelocytes. In the thickened submucosa there were larger groups of myelocytes.

The carnified area in the right upper pulmonary lobe was made up of alveoli, some of which were filled by hyaline fibrin, while others contained cellular granulation tissue. In many places, the organization of the exudate had advanced so far as to obscure the alveolar outlines. Between the fibrocytes occupying the alveolar spaces were groups of from ten to twenty-five large round cells with round, light-

stained nuclei and fine, purple-pink granulation. Oxydase stain demonstrated numerous granules in these cells. Some of the cells were undergoing mitotic division. The other organs, pancreas, suprarenal glands, kidneys, etc., were free from myeloid tissue.

CASE 10.—*Gumma of the Lung and Metastases of a Melanoblastoma of the Eye to the Liver in a Case of Acute Myeloblastic Leukemia.*—A Rumanian, aged 74, had his left eye removed for a pigmented tumor. A year later he entered the hospital with the complaint of severe pains in the mouth. The temperature was 99.6 F.; the pulse rate, 96; the respiratory rate, 20. The blood pressure was 120 systolic and 50 diastolic. In addition to severe gingivitis, clinical examination revealed a brownish-red macular and papular rash over the chest and abdomen, hyperresonance of the lungs with numerous râles, and enlargement of the heart to the left. Smears taken from the mouth showed many streptococci, but no fusiform bacilli or spirochetes. The Kahn and Wassermann reactions were three plus.

The erythrocyte count was 2,670,000; the hemoglobin content was 50 per cent. The white cell count was 50,800, with myeloblasts 80, neutrophils 4, monocytes 1 and lymphocytes 15 per cent. Dental and oral hygiene improved the condition of the mouth, but the rash on the body became widely spread. The course was afebrile but marked by rapidly progressing weakness. The patient died after a stay in the hospital for sixteen days. The duration of the illness had been four and a half weeks.

Autopsy: Post mortem, numerous slightly elevated, firm nodules, from 1 to 4 mm. in diameter, were found in the skin of the neck and the upper half of the chest. The nodules, which seemed to be located in the cutis, had the same color as the skin, namely, a light gray-brown. In the left cubital fossa and over the volar aspect of both arms, many pinhead-sized hemorrhages were present. The left eye was replaced by a prosthesis. In both groins and axillae, firm, discrete lymph nodes, ranging in size up to that of a chestnut, could be felt. The teeth were in poor condition, and the mucosa of the mouth was pale. The heart weighed 510 Gm. Underneath the epicardium and endocardium of both ventricles, there were many flat, grayish-white, discrete and confluent nodules, which measured from 1 to 5 mm. in diameter. Similar nodules could be seen in the wall of the pulmonary conus. Syphilitic aortitis was present, involving the aortic valve and causing moderate insufficiency of the valve. There was a small aneurysm of the descending aorta below the origin of the left subclavian artery. Emphysema of the lungs was present. In the center of the left lower lobe there was a sharply circumscribed, ovoid nodule 25 by 12 by 10 mm. in diameter. The nodule consisted of an opaque, yellow-gray center and a dense, fibrotic, deep-gray periphery. It was closely adjacent to, but separated from, a bronchus of the third order.

The spleen weighed 500 Gm. The liver weighed 1,670 Gm. The surface was studded by many whitish, dark brown and black nodules, which ranged from the size of a pinpoint to a diameter of 40 mm. The pigmented nodules were larger and more numerous than the white ones. On the sectioned surface, the same nodules were visible and occupied about one fifth of the parenchyma. The intervening hepatic tissue was gray-brown. There were hemorrhages in the mucosa of the lower part of the ileum and in the ascending colon. There were small whitish nodules in the cortex in both kidneys. The abdominal lymph nodes were enlarged and light purple. The bone marrow was light red-gray and soft. The brain weighed 1,140 Gm. It was very pale and moist. The retrobulbar tissue of the left side was free from tumor tissue.

Histologic Observations: In the bone marrow, the predominating type of cell was a large lymphoid round cell with ample, homogeneous, basophilic cytoplasm. The nuclei were round or slightly indented and contained a few small chromatin granules and several distinct nucleoli. A few of the cells showed fine, purple-pink granulation. There were numerous mitoses. Scattered between these cells were small foci of erythropoiesis with erythrogonias, erythroblasts and normoblasts. Other cell forms were scanty. There were few mature oxyphilic leukocytes, single plasma cells and occasional neutrophilic leukocytes with shrunken nuclei. The cords of the splenic pulp were uniformly composed of the large lymphoid cells found

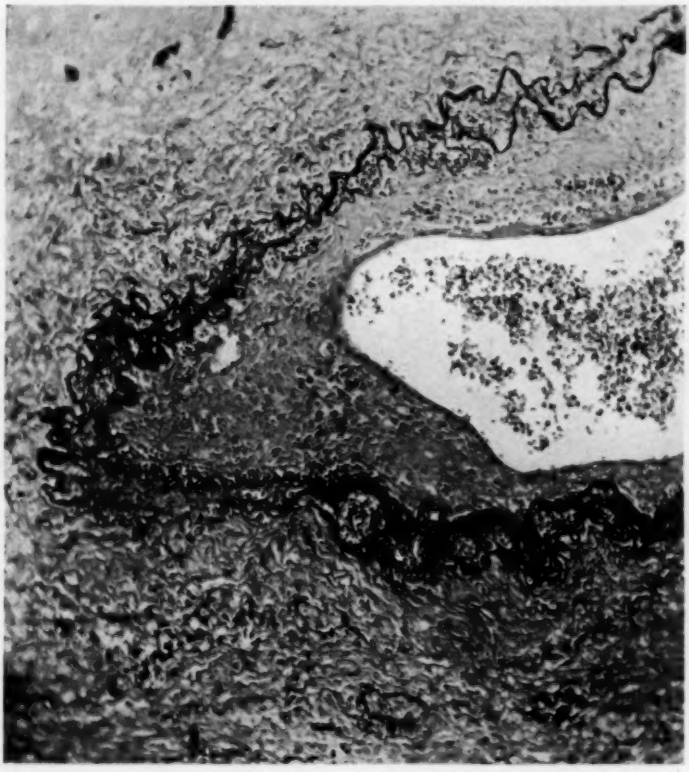

Fig. 8 (case 10).—Artery near the gumma in the lung. In the thickened intima, numerous immature blood cells are to be seen; elastic stain; × 300.

in the bone marrow. The follicles were small and lymphocytic. The large lymphoid cells had also replaced most of the lymphatic tissue of the abdominal and inguinal lymph nodes, the secondary follicles being reduced to small groups of lymphocytes.

The dark brown and black nodules of the liver consisted of elongated spindle-shaped cells, which were filled by dark brown pigment granules. The cells formed small alveoli, which were surrounded by a scanty stroma. In addition to the elongated cells, there were single large elements of irregular shape, which were so densely packed by pigment granules that the nucleus was completely obscured. The white nodules showed an entirely different picture. They were formed by the

basophilic round cells previously described, about one fourth of which gave a positive oxydase reaction. The pigmented and nonpigmented nodules occasionally fused together, and the two different types of cells mingled with each other. Lymphoid cells and pigmented cells could be seen lying side by side without interfering with their respective proliferations. The lymphoid cells were also present in the portal capillaries and in the periportal septums. Many of the Kupffer cells contained melanotic pigment, which was also found in some of the hepatic cells. An interesting finding were cylinders of melanotic pigment in the perivascular lymph spaces and in the intercellular bile capillaries.

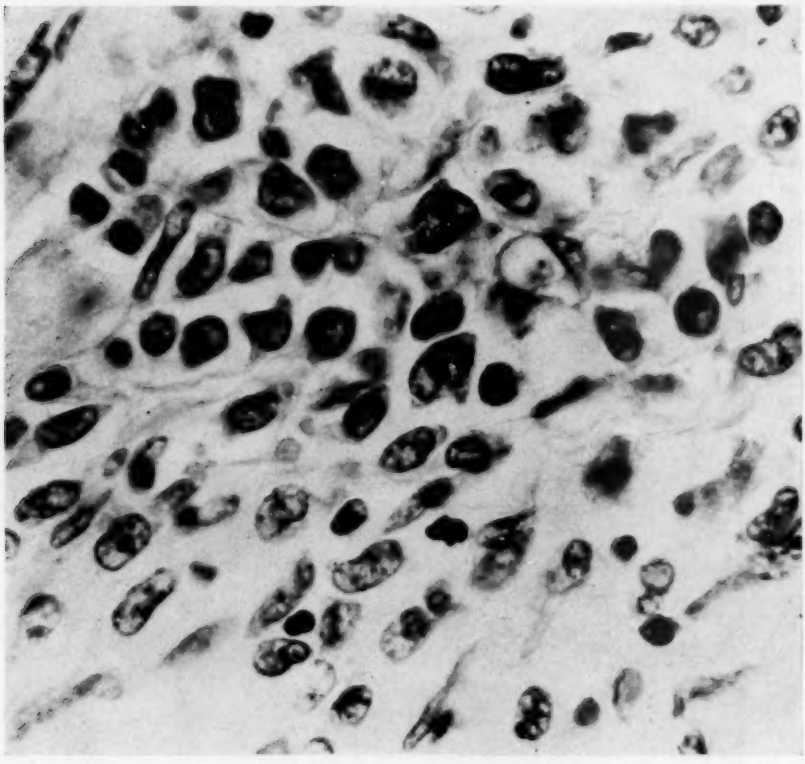

Fig. 9 (case 10).—Group of young myelocytes in the intima of the artery shown in figure 8. Note the reticulum between the myelocytes; × 1,200.

The nodules in the heart and skin were composed of lymphoid round cells, about half of which were oxydase-positive. In the skin, the cells were located in the papillary and reticular layer of the cutis and were separated from the epidermis by a band of hyaline tissue. The cells often accumulated about sebaceous and sweat glands. The nodules in the kidneys, too, were made up of these cells.

The nodule in the left lobe of the lung contained a necrotic center, which was surrounded by a capsule of connective tissue with small accumulations of lymphocytes and plasma cells. In the necrotic area, the outlines of blood vessels with much thickened walls and occluded lumen were discernible. Bielschowsky-Maresch silver impregnation demonstrated many argentaphil fibrils in the necrotic areas,

which, according to Coronini, is characteristic of a gumma. Adjacent to and extending into the node there were several small veins and arteries the intima of which was much thickened, and the adventitia and media of which were infiltrated by small round cells. The intima appeared very cellular, but the cells were of different character as compared with those in the media and adventitia (fig. 8); they possessed ample, basophilic cytoplasma and round or bean-shaped nuclei. The cytoplasm often contained fine, purple-pink granulation, especially near the nucleus. These cells spread apart the connective tissue fibrils of the intima, which became transformed into a reticulum. The fibrocytes increased in size, and their cytoplasm assumed basophilic coloration, while the nuclei resembled the nuclei of the cells in the meshes of the reticulum (fig. 9). There were no other changes in the lung, except an occasional group of large lymphoid round cells about a small blood vessel. The histologic picture of the aorta was that of typical syphilitic aortitis with advanced scarring.

## COMMENT

Of the three patients with lymphatic leukemia, two had responded to an acute infection like normal persons, namely, by the production of a leukocytic exudate. The unusually severe reaction to the anemic splenic infarct in the second case could be explained by the presence of streptococci in the infarcted area. The port of entrance of the streptococci was apparently the sore throat from which the patient had been suffering shortly before his death. In these two cases, the bone marrow contained myelocytes, and especially in the second observation the myelocytes were found in active proliferation and originating from undifferentiated cells about the blood vessels. In chronic lymphatic leukemia, small groups of myelocytes are usually present in the bone marrow (Naegeli, Helly [16]), and it is not uncommon to find single immature granulocytes in the peripheral blood in these cases (Priesner [17]). According to Piney,[18] the myeloid tissue surrounds the accumulations of lymphatic cells much as it surrounds the metastases of malignant tumors to the bone marrow. In this observation, Piney saw a support for his conception that leukemia belongs to the true tumors. Banti [19] distinguished four stages of the bone marrow changes in lymphatic leukemia, namely, hyperemia, hematopoiesis, nodular proliferation and diffuse proliferation of the lymphatic tissue. Myeloid tissue, however, is found not only in the third but also in the fourth stage, and it seems to me that the active proliferation of granulopoietic tissue in a diffusely lymphatic bone marrow rather speaks against the tumor theory. In acute lymphatic leukemia, too, foci of myelocytes are found in the bone marrow.

16. Helly, K.: Leukaemien, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, vol. 1, pt. 2, p. 1015.

17. Priesner, E.: Wien. klin. Wchnschr. **43**:170, 1930.

18. Piney, A.: Am. J. M. Sc. **169**:691, 1925.

19. Banti: Le leucémie, Atti d. VIII. riun. d. Soc. ital. di patol., 1913.

The granulopoietic tissue was not restricted to the bone marrow. In the first case, myelocytes could be detected also in the splenic pulp, while in the second case they were observed in the spleen, in the liver and, particularly, in the abdominal lymph nodes, the sinuses of which contained numerous streptococci. Naegeli, who described myelocytes in the lymph nodes in cases of lymphatic leukemia, considered them as compensatory for the lymphatic replacement of the bone marrow. Thus, in the first two observations, sufficient myeloid tissue was present to supply granulocytes for a leukocytic exudate.

The third patient, who had subacute aleukemic lymphadenosis changing later into the leukemic form, reacted differently to a complicating infection which was followed by streptococcic septicemia. Under the influence of the septicemia, the white count dropped within a few days from 53,000 to 850 and, save for the severe anemia, the blood picture resembled finally an agranulocythemia. About the necrotic lesions in the mouth there was not a single granulocyte, and the lymphatic elements were unable to compensate for the lack of leukocytic response. Nowhere in the body were there any myelocytes. In the bone marrow, only an occasional large oxyphilic leukocyte was found, and the lymph nodes showed a few myeloblasts. In the lymph nodes and in the spleen, the leukemic cells revealed very severe regressive changes, which caused a peculiar loosening of the structure of these organs. In the bone marrow and in the liver, the disintegration of the cells was much less marked. A. Schultz,[20] who described septicemia in a case of aleukemic lymphadenosis turning into the leukemic stage, was struck by the complete absence of mesenchymatous reaction in this case as compared with other cases of septicemia.

In two cases of myeloid leukemia complicated by acute infections, the immature granulocytes took little part in the local defense reactions, while mature granulocytes were abundant. It is interesting that the prostatic abscesses contained only 5.5 per cent myelocytes, while these cells were much more numerous in the interstitial infiltrations. The severe diphtheritic colitis in the chronic myelosis with terminal acute exacerbation was undoubtedly due to the intensive roentgen treatment. I have repeatedly seen these severe inflammations of the descending and sigmoid colon as the result of continued irradiation of the spleen. In spite of the 81 per cent myelocytes in the peripheral blood, mature granulocytes only were found underneath the necrotic membrane of the colon.

In this group of cases, too, there is one which is characterized by the lack of defense reaction. This case belongs to the type of leukemia that is usually called stem cell leukemia because the cells are so undiffer-

20. Schultz, A.: Krankheitsforschung **8**:206, 1930.

entiated that they cannot be identified with certainty. Since the organic changes resembled those found in myelosis, I have included this case among those of myeloid leukemia. The scarcity of myelocytes in the bone marrow readily explains the absence of granulocytes from the inflammatory lesions. In the tonsils and larynx there was practically no reaction to the necrosis, and in the pneumonic areas only a few stem cells had entered the alveoli.

In three cases of myeloid leukemia, fibrinous exudation with organization was found. The organizing granulation tissue produced blood cells, the origin of which could be studied best in the two cases of fibrinous pericarditis. In one case I have referred to a spongy syncytium located underneath the fibrinous membrane and giving rise to myelocytes and normoblasts. This syncytium answers to Hueck's [21] description of the most primitive form of mesenchymatous tissue. According to Hueck, the basic structure of the embryonic mesenchyma is a sponge composed of protoplasmic septums with nuclei in the knots, and of pores filled by tissue fluid. By differentiating fibrils on the free surface of the protoplasmic septums and keeping the pores open, reticular tissue is formed, while fibrillar connective tissue results from the filling of the pores by fibrils and ground substance. The production of the blood cells starts with condensation and increased basophilia of the cytoplasm about the nuclei. The cells retract from the rest of the syncytium and come to lie free in the tissue fluid that fills the pores. Normally, in postembryonal life, the basic structure of the mesenchyma is obscured because the pores are filled with some kind of differentiated ground substance. Even during the neoformation of connective tissue the syncytial structure remains invisible because the production of fibrils dominates the picture from the beginning. There exists apparently an important difference between the normal mesenchyma and the mesenchyma of the leukemic person, which manifests itself when the mesenchyma is irritated. Though the irritated mesenchyma in leukemia may produce colagenous ground substance, it also possesses the property to develop into myeloid tissue by passing through the stage of the undifferentiated protoplasmic syncytium. Granulocytes and erythrocytes differentiate side by side from this syncytium, and there seems to be an early common stage corresponding to Maximow's hemocytoblast.

In case 8, the pericarditis was early, and the process of organization was in its beginning. The irritated fibrocytes were very large with deeply basophilic cytoplasm. They differed from the fibrocytes commonly seen in inflammation by a peculiar nuclear differentiation with prominent angular nucleoli and by their transformation into abnormal, huge granulocytes. This skipping of the hemocytoblast stage during

21. Hueck, W.: Beitr. z. path. Anat. u. z. allg. Path. **66**:330, 1920.

the formation of granulocytes has been repeatedly described, and, especially in leukemia, specific and oxydase granules may appear in cell forms that are not yet separated. Stockinger [22] saw in this abnormal mesenchymal differentiation a disproportion between irritation and response.

One may question whether the large basophilic, granule-producing cells are fibrocytes and not histiocytes. It is true that the differentiation between these two types of cells, especially when irritated, may cause great difficulty, but it is the rich branching of the cells and their intimate relation to the ground substance that have induced me to consider them as fibrocytes.

Marchand's pupil, G. Herzog,[23] who advocated the local formation of granulocytes in inflammation from adventitial elements, described a case of uremic pericarditis with production of granulocytes in the subepicardial tissue. He depicted the formation of granules in large adventitial cells, but saw also immature granulocytes in the lumen of the dilated blood vessels. Since he did not give the blood findings or the histologic changes in the other organs, it is difficult to draw any conclusions from his case. I have examined a number of pericarditides, in particular the uremic form, but so far have been unable to find evidences of local granulopoiesis.

In the case of myelosis with chronic pneumonia, the extramedullary myelopoiesis was restricted chiefly to the spleen and abdominal lymph nodes. In the area of organization of the pneumonic exudate, groups of young myelocytes were scattered between the proliferating fibrocytes.

One of the most interesting observations is the combination of acute myeloblast leukemia with metastases of a melanoblastoma of the eye to the liver and a syphilitic granuloma of the lung. The combination of leukemia and malignant tumor is very rare (Hirschfeld,[14] Glückmann,[24] Lüder,[25] Marischler [26] and others), and it has been said that when a malignant tumor develops in a leukemic patient, the leukemic symptoms may regress (Zadek,[27] Marischler). In my case there was no interference between leukemia and tumor, and in the liver the two types of cells were found growing side by side.

The lesion in the lung was diagnosed as gumma because of its location in the center of the lower lobe, the vascular changes about the lesion, the presence of argentaphil fibrils in the necrotic area and the positive serologic reactions. The proliferated intima of the thickened

22. Stockinger, W.: Ztschr. f. d. ges. exper. Med. **58**:777, 1928.
23. Herzog, G.: Centralbl. f. allg. Path. u. path. Anat. **31**:481, 1921.
24. Glückmann, cited by Hirschfeld.[14]
25. Lüder, cited by Hirschfeld.[14]
26. Marischler: Wien. klin. Wchnschr. **9**:686, 1896.
27. Zadek, cited by Hirschfeld.[14]

vessels near the granuloma contained groups of young myelocytes, and between these myelocytes the connective tissue was transformed into a reticulum. Here, too, I obtained the impression that the myelocytes were formed locally, and that the fibrocytes acted as their parental cells. Against immigration from the blood spoke the fact that the myelocytes were most numerous near the internal elastic membrane, and that the subendothelial layer was free from these cells.

## CONCLUSIONS

From the histologic study of the inflammatory lesions found in ten cases of leukemia the following conclusions can be drawn:

Provided that some myeloid tissue capable of maturation is left, the leukemic organism reacts to an infection like a normal one. Even in a diffusely lymphatic marrow, the myeloid cells can proliferate, encroaching on the lymphatic tissue, when stimulated by an infection. The literature contains many observations dealing with the return of normal blood findings in leukemic patients during or after an intercurrent infection (Allacia,[28] Körmöczy,[29] Funk,[30] Naegeli,[8] Hirschfeld,[14] Dock [13] and others). These facts are difficult to reconcile with the conception that leukemia belongs to the malignant tumors. The restoration of a normal hematopoiesis in leukemia under the influence of an infection cannot be compared with the disappearance of an epithelioma of the skin over which erysipelas is spreading, since one is dealing not merely with a regression of the leukemic tissue but with the resumption of an exceedingly intricate function by the diseased organ.

If the granulopoiesis is completely exhausted, there is no defense reaction to an infection. I could not confirm the statements made by Dionisi [11] and Bickhardt [12] that the leukemic cells may take the place of the mature granulocytes, very few immature blood cells appearing in the inflamed area.

It is generally accepted now that the granulated cells of an exudate come from the blood, and any attempt that has been made to question Cohnheim's fundamental observation has been doomed to prompt refutation (Henke and Silberberg [31]). Extramedullary granulopoiesis, however, does occur under a variety of abnormal conditions, and though in some instances it may result from the colonization of immature bone marrow cells (Jaffé [32]), in the majority of the cases the cells are formed locally. It is beyond the scope of this article to enter into a discussion

28. Allacia, G. B.: Clin. med. ital. **12**:1, 1902.
29. Körmöczi: Folia haemat. **11**:297, 1911.
30. Funk, cited by Helly.[16]
31. Henke, F., and Silberberg, M.: Klin. Wchnschr. **11**:49, 1932.
32. Jaffé, R. H.: Beitr. z. path. Anat. u. z. allg. Path. **68**:224, 1920.

of the various theories on extramedullary myelopoiesis. I refer to the recent reviews by Maximow [33] and Lang.[34] Suffice it to say that in the normal organism the undifferentiated, potentially myelopoietic tissue is apparently located between the adventitial histiocytes about the smaller blood vessels and in the cellular reticulum of certain organs, where it is hidden because of its insignificant appearance (Maximow). The histiocyte and fibrocyte are unable to change into hemocytoblasts. In leukemia, however, the range of the cells that may develop into blood cells is much wider. In previous publications I have described the transformation of histiocytes into myeloid cells in cases of leukemia, and the observations on inflamed tissue have convinced me that also the fibrocyte may do so. Freund,[35] who studied the effect of x-rays on leukemic infiltrations of the skin, also came to the conclusion that the myeloid cells were derived locally from fibrocytes. On the other hand, I have been unable to find any evidences for a reversion of the leukemic cells into fibrocytes or for their transformation into other cells (macrophages). The modern literature contains many reports on such transformations obtained in vitro (Awrorow and Timofejewsky,[36] Timofejewsky and Benewolenskaja,[37] Verati,[38] Hirschfeld,[39] Hirschfeld and Rawidowicz,[40] Katsunuma,[41] Silberberg and Voit,[42] Bloom [43] and others). This discrepancy between the findings inside the body and in tissue culture shows again how careful one should be in drawing conclusions from observations made on explanted cells.

I have so far been unable to find morphologic evidences for a transformation of fibrocytes into lymphocytes. Since lymphadenoid tissue is present practically everwhere in the body, this question will be difficult to decide. In this connection it may be mentioned that, in lymphatic leukemia, infiltrations not seldom develop in cutaneous scars, especially those after herpetic lesions and burns (Halle [44]).

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33. Maximow, A.: Bindegewebe und blutbildende Gewebe, in von Möllendorff, M.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 2, pt. 1.

34. Lang, F. J.: Folia haemat. **43**:95, 1931.

35. Freund, F.: Virchows Arch. f. path. Anat. **369**:501, 1928; Klin. Wchnschr. **7**:977, 1928.

36. Awrorow, P., and Timofejewsky, A.: Virchows Arch. f. path. Anat. **216**:184, 1914.

37. Timofejewsky, A., and Benewolenskaja, S. W.: Virchows Arch. f. path. Anat. **263**:719, 1927; Arch. f. exper. Zellforsch. **8**:1, 1929.

38. Veratti, cited by Gloor, W.: Folia haemat. **45**:267, 1931.

39. Hirschfeld, cited by Silberberg and Voit.[42]

40. Hirschfeld and Rawidowicz, cited by Silberberg and Voit.[42]

41. Katsunuma, S.: Tr. Jap. Path. Soc. **19**:258, 1929.

42. Silberberg, M., and Voit, K.: Deutsches Arch. f. klin. Med. **171**:110, 1931.

43. Bloom, W.: Arch. f. exper. Zellforsch. **11**:145, 1931.

44. Halle, H.: Arch. f. Dermat. u. Syph. **159**:238, 1930.

The microscopic findings in inflamed tissue again demonstrate the sharp separation between the lymphopoietic and the myelopoietic tissue. Never was I able to find any indications of a transformation of leukemic lymphatic cells into hemocytoblasts and granulocytes, and whenever in lymphatic leukemia the body mobilized granulocytes it resorted to the undifferentiated germinal tissue about the blood vessels. It is significant that in spite of the abundant proliferation of the lymphatic tissue the undifferentiated cells have retained their granulopoietic properties. As far as the inflammatory reactions are concerned, there is no difference between the acute and chronic leukemias, which speaks against the conception held by C. Sternberg, and others that these two diseases do not belong together.

SUMMARY

The histologic pictures of the inflammatory defense reactions in ten cases of leukemia are given. It has been shown that the type of response depends on the presence of myeloid tissue able to produce mature granulocytes. In the presence of such tissue, the leukemic patient reacts to an infection like a normal person, while in the absence of such tissue the leukemic cells are not able to compensate, and the alterative changes predominate as they do in agranulocythemia and aplastic anemia. It seems that for the leukemic organism von Möllendorff's conception of the myelopoietic potencies of the fibrocyte holds true.

# METABOLISM IN ACUTE MOLECULAR DEGENERATION OF STRIATED MUSCLE

## III. VARIATIONS PRODUCED IN THE GLYCOGEN, LACTIC ACID AND PHOSPHORUS OF THE MUSCLE

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AND
H. R. FISHBACK, M.D.
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Carbohydrate metabolism in normal striated muscles involves many substances in complex interrelationships. Present views of these physiologic functions are presented by Meyerhof,[1] Hill,[2] Fiske and Subbarow[3] and Parnas.[4]

However, the changes of metabolism in pathologic conditions of muscle in the body have been investigated but little. We are concerned in this paper with acute molecular degeneration of striated muscle, especially as to its effect on certain factors of carbohydrate metabolism.

The work was carried out on rabbits, in the muscles of which acute molecular degeneration had been induced by a standard, easily controlled method previously described by us.[5] In addition, several rabbits were used for the study of variations in the glycogen and lactic acid of the muscles as produced in the lesser injury of freezing. In these animals, the muscles were frozen solidly with carbon dioxide snow, allowed to thaw spontaneously at room temperature and removed forty-eight hours later. The animals were young, healthy stock on an ordinary mixed diet. Both the injured and the control animals were made to fast for forty-eight hours before removal of the muscles, but were given water freely. They were kept in individual small cages that restricted activity.

Degenerated muscles were removed in the acute, florid stage of the process, from twenty-four to forty-eight hours after injury. With the

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From the Department of Pathology, Northwestern University Medical School.

1. Meyerhof, O.: Chemical Dynamics of Life Phenomena, Philadelphia, J. B. Lippincott Company, 1924.

2. Hill, A. V.: Physiol. Rev. **2**:310, 1922.

3. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **81**:629, 1929.

4. Parnas, J. K.: Compt. rend. Soc. de biol. **101**:37, 1929.

5. Fishback, D. K., and Fishback, H. R.: Am. J. Path. **8**:211, 1932.

animal anesthetized by iso-amyl-ethyl barbituric acid, the muscle was removed after having been frozen *in situ* by a slush of carbon dioxide snow and ethyl chloride, according to the method of Davenport and Davenport.[6] It was then finely sliced while frozen hard and transferred to the required fluids for further chemical procedures, as described later.

Glycogen, lactic acid and phosphorus compounds were determined, since they represent important factors in carbohydrate metabolism in muscle. These will be considered separately in the following sections of this report.

### GLYCOGEN

*Methods.*—About 1 Gm. of the finely sliced carbon dioxide-frozen muscle was weighed carefully and rapidly into ice-cold 60 per cent potassium hydroxide, and the mixture was shaken thoroughly. The quantitative determinations, of glycogen were made by the method of Pflüger,[7] with determinations of sugar on the final hydrolyzed samples by Somogyi's modification [8] of the Shaffer-Hartmann procedure.[9]

*Results.*—As represented in chart 1, the glycogen values obtained for the control animals vary considerably, but fall within a comparatively high range, with a maximum of 726, a minimum of 450 and an average of 567 mg. per hundred grams. Similar variability in normal muscle was reported by Handovsky and Westphal,[10] and by Davenport, Davenport and Ranson.[11] The high value, 953 mg., shown in the control group, was obtained on a rabbit that had not previously been made to fast and was not used in calculating the group average. It shows the effect of recent ingestion of food on the storage of glycogen in muscle.

With injury produced by previous freezing of the muscle there was a definite decrease of the glycogen store to a range of from 175 to 367 mg. per hundred grams. Mechanical trauma reduced the glycogen level still more, to the very low average of 104 mg. per hundred grams, the lowest value being 60 mg. Microscopic study of the degenerated muscles demonstrated structural changes of much greater severity in the mechanically injured muscles than in the frozen ones.

In the muscle injury studied here, the major blood vessels were found to be intact, although there was some capillary injury.[5] Thus

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6. Davenport, H. A., and Davenport, H. K.: J. Biol. Chem. **76**:651, 1928.
7. Pflüger, E.: Arch. f. d. ges. Physiol. **129**:362, 1909.
8. Somogyi, M.: J. Biol. Chem. **70**:599, 1926.
9. Shaffer, P. A., and Hartmann, A. F.: J. Biol. Chem. **45**:365, 1921.
10. Handovsky, H., and Westphal, K.: Arch. f. d. ges. Physiol. **220**:399, 1928.
11. Davenport, H. A.; Davenport, H. K., and Ranson, S. W.: J. Biol. Chem. **82**:499, 1929.

the circulation was ample to nourish and keep the tissue alive. This type of experiment on muscle, with the general body relationships of the latter undisturbed, avoids the objections to metabolic experiments on extirpated muscles, in which systemic regulatory factors have been eliminated.

The injured muscle was not used by the animal, but the effect on the glycogen store of keeping the muscle at rest was negligible. Daven-

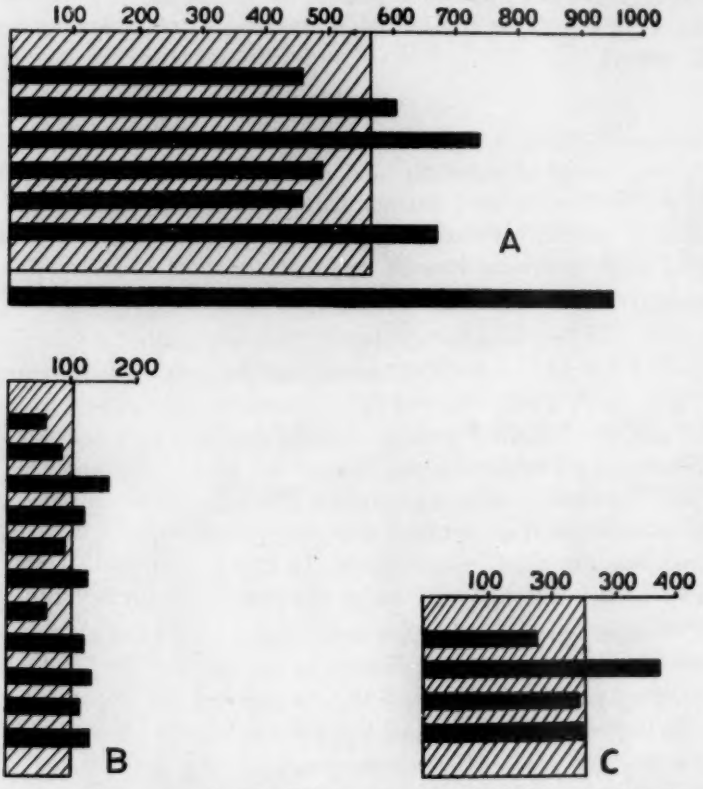


Chart 1.—Glycogen content (milligrams per hundred grams) of (*A*) control muscles, (*B*) contused muscles and (*C*) frozen muscles. The solid black rectangles represent individual values; the rectangles of diagonal lines, the group averages.

port, Davenport and Ranson,[11] working on muscle contracture, found no lowering of glycogen reserve from lack of contractile activity.

Many general systemic occurrences may alter the glycogen store of the muscles. Among these are general fatigue, fasting and hyperpyrexia, with lowering of the sugar supply. The same effect is obtained by administering thyroid, insulin or strychnine. Postmortem change in the muscles is associated with rapid loss of glycogen. A decrease of glycogen in the muscles is found with diabetes.

Experimentally, local fatigue of the muscle has been found to decrease the glycogen store.[12] Davenport, Davenport and Ranson,[11] working with experimental tetanic contracture of the hind legs of animals, found varied amounts of glycogen in different stages of the contracture in innervated muscles, but no alteration of the amounts of glycogen in denervated muscles. Denervation likewise protects the muscle against loss of glycogen, according to Wertheimer,[13] even in fasting, which causes general lowering of the level of muscle glycogen otherwise.

In this acute molecular degeneration of muscle there is found in every instance a rapid primary glycogenolysis, with a resultant low value on quantitative examination. The maintenance of glycogen at this low level for forty-eight hours or more with an adequate supply of sugar offered in the blood indicates probable depression of the glycogenic function, or of the glycogen-storing capacity of the injured muscle, in addition to the early glycogenolysis.

### LACTIC ACID

*Methods.*—The finely sliced frozen muscle was extracted for ten minutes in ice-cold 5 per cent trichloracetic acid. Lactic acid was determined on the filtrate by the method of Friedemann, Cotonio and Shaffer,[14] with Davenport's modification [6] for small amounts of tissue.[15]

*Results.*—The results are shown graphically in chart 2. In the control animals, the lactic acid content of the muscles averaged 17.3 mg. per hundred grams. In some of the earlier work, in which iso-amyl-ethyl barbituric acid alone was used to produce anesthesia, values ranged to almost 22 mg. Later, intraspinal injection of procaine hydrochloride was added, with the result that relaxation of muscles was complete, and the lactic acid values were lowered to around 15 mg. In the degenerated muscle, however, this factor was not significant, since the animal kept the injured parts motionless.

In the degenerated muscles there was marked increase of lactic acid. In those injured by freezing, the lactic acid reached an average value of 48 mg. per hundred grams, or an increase of 175 per cent over the average control value, and in those injured by mechanical trauma, it reached 64.6 mg., or an increase of 275 per cent.

Lactic acid is present in muscles normally as an intermediate product of sugar catabolism. According to Meyerhof,[16] the reaction dextrose→

12. Olmsted, J. M. D., and Coulthard, H. S.: Am. J. Physiol. **84**:610, 1928.
13. Wertheimer, E.: Arch. f. d. ges. Physiol. **215**:779, 1927.
14. Friedemann, T. E.; Cotonio, M., and Shaffer, P. A.: J. Biol. Chem. **73**:335, 1927.
15. Dr. Davenport loaned us his apparatus and gave valuable suggestions.
16. Meyerhof, O.: Lancet **2**:1415, 1930.

lactic acid is reversed during the stage of recovery of normal contractility, with reformation of part of the sugar.

Many procedures, such as mild exercise or slight interference with venous drainage from the muscle, cause increased formation and accumulation of lactic acid in the normal muscle. In muscles removed from the body, lactic acid accumulates rapidly. The rate of this formation of lactic acid is increased by trauma, such as cutting or grinding the muscle. In hashed muscle or extracts of muscle there is active

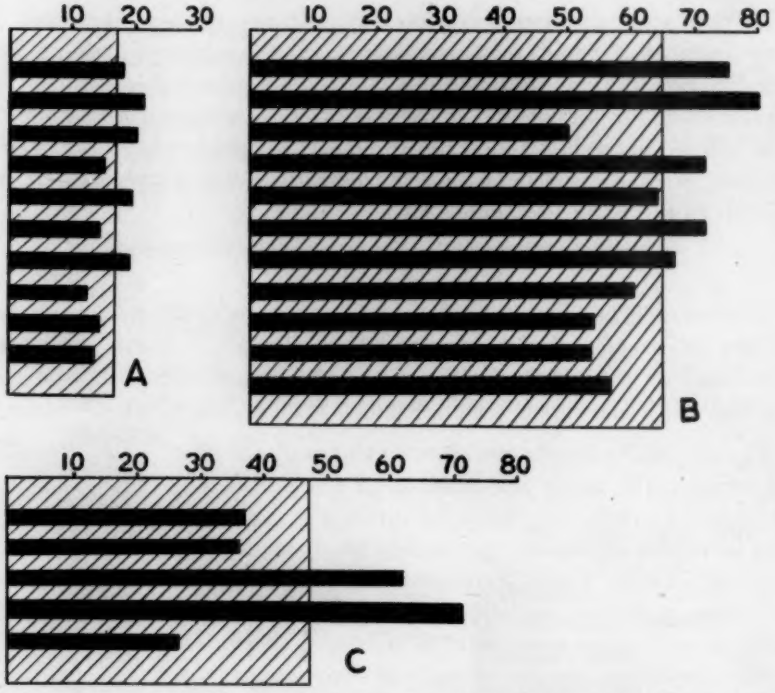


Chart 2.—Lactic acid content (milligrams per hundred grams) of (*A*) control, (*B*) contused and (*C*) frozen muscles. The solid black rectangles represent individual values; the rectangles of diagonal lines, the group averages.

glycolytic capacity, and on incubation of such digests large quantities of lactic acid may be found.[17] In an untraumatized muscle in vitro, such as a gastrocnemius of the frog, the rate of formation of lactic acid may be accelerated by stimulating the muscle to contraction. Abnormal accumulation of lactic acid may occur in the muscles of the living

17. (*a*) Embden, G.; Kalberlah, W., and Engel, H.: Biochem. Ztschr. **45**:45, 1912. (*b*) Meyerhof, O.: ibid. **183**:176, 1927. (*c*) Davenport, H. A., and Cotonio, M.: J. Biol. Chem. **73**:463, 1927. (*d*) Stiven, D.: Biochem. J. **23**:583, 1929.

animal with extreme fatigue [18] or with stasis of venous blood.[19] After death there is likewise an abnormal accumulation of lactic acid in the muscles, which is, according to Meigs,[20] an important factor in the causation of muscle rigor.

An active rôle is ascribed to lactic acid by Wells [21] in the production of Zenker's degeneration of muscle. In this study, we have applied the name "acute molecular degeneration of muscle," as previously suggested,[5] to cover the degenerative changes of muscle which include "waxy degeneration" as one phase. Such degeneration is undoubtedly constantly associated with increase in lactic acid, but the order of increase is not as high as may be found, in fatigue or post mortem, for instance, without degeneration of muscle cells.

The accumulation of acid in these injured muscles in amounts maintained well beyond normal values indicates damage to the metabolic function, with a resulting incomplete cycle of carbohydrate change. The process would doubtless reach an equilibrium at a far different level of substrate and products, as in digests of muscle hash, except for the variable factors introduced by the circulating blood.

### PHOSPHORUS COMPOUNDS

*Methods.*—Phosphocreatine and inorganic phosphorus were determined by the method of Fiske and Subbarow [3] on the trichloracetic acid extract of the muscle. (See section on lactic acid.) The addition of the carbon dioxide-frozen muscle to the cold trichloracetic acid lowered its temperature below the freezing point of water, so that ice formed on the outside of the extraction flask. The ice-cold extract was filtered quickly into an iced receptacle containing enough saturated alkali to slightly alkalinize the filtrate, in order to minimize the hydrolysis of phosphocreatine.

*Results.*—In chart 3, the values shown for phosphocreatine in the control animals range within rather narrow limits, from 61 to 72 mg. per hundred grams, with an average of 68 mg. The inorganic phosphorus values of 30 to 37 mg. likewise show but little variation from the average of 34 mg.

In the degenerated muscles there is a marked drop of phosphocreatine to an average of 7 mg. per hundred grams. In carrying out determinations of the very low content of the injured muscles, a known amount of phosphate standard was added to the sample after the hydrolysis of the phosphocreatine, according to the suggestion of Fiske

18. Meyerhof, O., and Lohmann, K.: Arch. f. d. ges. Physiol. **204**:327, 1924.
19. Mendel, B.; Engel, W., and Goldscheider, I.: Klin. Wchnschr. **4**:307, 1925.
20. Meigs, E. B.: Am. J. Physiol. **26**:191, 1910.
21. Wells, H. G.: J. Exper. Med. **11**:1, 1909.

and Subbarow. Inorganic phosphorus values of the injured muscles showed only a slight inconstant increase over control values, with an average of 37 and a range of from 32 to 45 mg. per hundred grams.

The low phosphocreatine is the most marked feature in the altered phosphorus metabolism of the injured muscles. Similar levels have been reported also for muscles that were stimulated to contraction to the state of fatigue.[22] With time allowed for recovery, and with blood circulation intact, the phosphocreatine of fatigued muscles rather rapidly

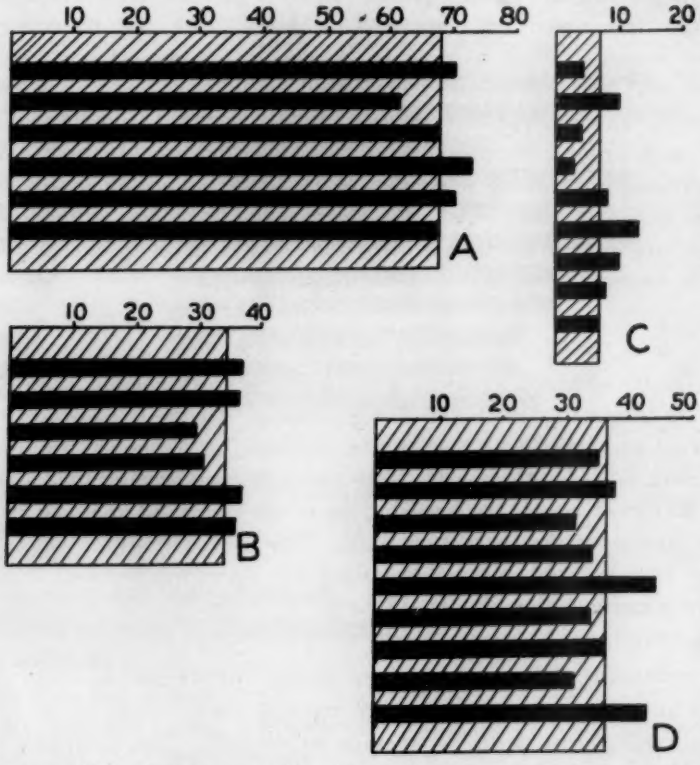


Chart 3.—(*A*) Organic and (*B*) inorganic phosphorus content of control muscles (milligrams per hundred grams); (*C*) organic and (*D*) inorganic phosphorus content of degenerated muscles. The solid black rectangles represent individual values; the rectangles of diagonal lines, the group averages.

recovers. In fatigue, then, the low values may be explained as the driving of the reaction in the direction of hydrolysis of phosphocreatine with insufficient time for the reverse process, or recovery, to occur.[23]

22. (*a*) Irving, L., and Bastedo, G. M.: Am. J. Physiol. **86**:225, 1928. (*b*) Dixon, H. H.; Davenport, H. A., and Ranson, S. W.: J. Biol. Chem. **82**:61, 1929. (*c*) Fiske and Subbarow.[3]

23. Meyerhof, O., and Nachmansohn, D.: Biochem. Ztschr. **222**:1, 1930.

The factor of time is not significant, however, in explanation of the low values in injuries that are 48 hours old, far longer than the short period of recovery in uninjured fatigued muscles. Since there is also an ample supply of blood to these injured muscles,[5] the cause of the impaired phosphocreatine balance must be in the altered metabolism of the pathologic muscle cells themselves.

Inorganic phosphorus amounts remain close to the control values. This is quite different from the results reported for incubated muscle hash, muscle extract or expressed juice of muscle,[24] in which the decrease in phosphocreatine is associated with a corresponding increase in inorganic phosphorus. Probably the latter values represent the end-result or equilibrium in a closed system, which would not be likely to be reached in the body, with the number of variable factors introduced by the circulating blood.

Under anaerobic conditions in muscle, according to Meyerhof,[16] phosphagen hydrolyzes without increase in inorganic phosphorus, the new-formed phosphoric acid being combined with hexose. In these injured muscles, even with sufficient supply of blood, it is still possible that within the individual units of degenerated muscle fibers anaerobic conditions may have prevailed.

It does not seem likely that any significant increase in inorganic phosphorus has been lost by diffusion out of the injured muscles in the given period. Further, so far as loss by circulation is concerned, it was stated by Irving and Bastedo [22a] that even though twice the blood content of inorganic phosphorus was formed in a muscle, no increase in inorganic phosphorus could be found in the venous drainage.

## COMMENT

In this acute injury of muscle the degenerative lesion is diffuse and extensive. Metabolic function might be expected to be disordered in keeping with the morphologic changes, when such changes are found to involve the parenchymatous cells.

The marked decrease in glycogen, the rise of lactic acid, and the fall of phosphocreatine are evidence of disturbance of the cycle of reactions in sugar metabolism.

The trend of the reaction is the same as in digests of muscle hash or muscle extract. It might be inferred that the variation from the normal metabolism in acute molecular degeneration of muscle is brought about by enzyme activity which is freed from the control usually exerted by the living cell over these intracellular functions.

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24. Beattie, F., and Milroy, T. H.: J. Physiol. **60**:379, 1925; **62**:174, 1926. Embden, G., and Haymann, C.: Ztschr. f. physiol. Chem. **137**:154, 1924. Meyerhof.[17b] Davenport.[17c]

Since the normal muscle metabolism plays an important rôle in the maintenance of body heat, extensive injury of muscle in disease, with a lowering of the easily combustible carbohydrate store of the muscles, may well be a serious factor in the body economy. The acute molecular degeneration ocurring with typhoid fever may thus be a factor in the pronounced asthenia and subnormal temperature of the convalescence. The same may be true in other severe acute infections [25] in which acute molecular degeneration of muscle has been found. In this connection, pure speculation would suggest still further that variable degrees of disturbance of muscle cell metabolism may exist in the body in disease, with morphologic changes not demonstrated by the present crude technic.

## SUMMARY

A uniform acute molecular degeneration of muscles produced in rabbits has been found to be associated with alteration of the muscle metabolites.

Muscle glycogen dropped consistently from a control value of 567 mg. per hundred grams to an injury average of 104 mg. per hundred grams.

There was a marked rise of lactic acid from the control average of 17.3 mg. to 64.6 mg. per hundred grams.

Phosphocreatine decreased from the control average of 68 mg. to 7 mg. per hundred grams. Inorganic phosphorus varied slightly and irregularly from the control value, with a slight tendency toward increase.

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25. Stenström, B.: Arch. Path. **3**:361, 1927. Stemmler, W.: Virchows Arch. f. path. Anat. **216**:57, 1914.

# Laboratory Methods and Technical Notes

## A SIMPLE METHOD FOR THE STUDY OF THE SPORULATION OF COCCIDIAL OOCYSTS

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The sporulation of coccidial oocysts is one of the most important criteria of exogenous development of parasites, and at the same time is of importance in the identification of the different genera of coccidia. Therefore, this test is extensively applied in laboratory practice. The methods of the test must include consideration of the optimum conditions of sporulation of the oocysts. At present these conditions are known sufficiently, as far as general points of view are concerned, but much less in their details.

Generally a sufficiently high temperature, sufficient humidity and the presence of oxygen are regarded as absolutely necessary for abundant and quick sporulation.

The more common methods of testing the sporulation of coccidial oocysts aim to correspond to these conditions as far as possible. However, they show some differences. The method recommended by Nöller [1] of spreading the feces to be tested on some layers of humid filter paper in a Petri dish allows undisturbed exposure to oxygen, and by the cover of the Petri dish desiccation is prevented or delayed. Kept at room temperature, the oocysts, with this method, show abundant sporulation, mostly within two or three days. In another method widely used for testing the sporulation of oocysts, as mentioned by Pérard,[2] Tyzzer,[3] Henry,[4] Becker and Crouch [5] and others, the feces to be tested are suspended in a 2.5 per cent solution of potassium dichromate, which prevents decomposition, on the one hand, and acts as an oxidizing reagent on the other. Also by this method the oocysts usually develop spores within two or three days.

In my investigations, in the course of which both these methods were used, the following manner of observing the sporulation proved to be more satisfactory and useful, especially in serial experiments in which the interest centered on the microscopic examination.

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From the Department of Animal Pathology and Hygiene, University of Nebraska.

1. Nöller, W., in Stang and Wirth: Tierheilkunde und Tierzucht, Berlin, Urban & Schwarzenburg, 1928.

2. Pérard, C.: Compt. rend. Acad. d. sc. **179**:1436, 1924.

3. Tyzzer, E. E.: Am. J. Hyg. **10**:269, 1929.

4. Henry D. P.: Univ. California Publ., Zool. **36**:157, 1931.

5. Becker, E. R., and Crouch, H. B.: Proc. Soc. Exper. Biol. & Med. **28**:529, 1931.

### METHOD

The feces containing the oocysts are spread thinly on the surface of a plain agar solution, poured and solidified in Petri dishes. The agar used for this purpose is a simple solution in distilled water commonly used for bacteriologic mediums. In order that the correct degree of humidity of the medium may be secured, the amount of agar to be dissolved in distilled water has to correspond to its degree of solidification, which varies a little in the different commercial brands of agar. In my investigations, in which Bacto-agar (Difco standardized) was used, an amount of from 0.8 to 1 per cent proved to be sufficient. This agar is moist enough to favor sporulation, but also solid enough to allow an easy spreading of the feces on its surface. The humidity that gathers on the surface of the solid agar and on the cover of the Petri dish keeps the medium and the atmosphere moist during the period of examination. Addition of preservatives or of disinfectants has not been necessary.

At room temperature, the sporulation usually takes place within from twenty-four to forty-eight hours, as in the case of the other two methods described.

The advantage of the agar plate for testing sporulation in diagnostic and systematic serial examinations is that the preparation of smears as otherwise necessary for microscopic examination thus becomes superfluous. The Petri dishes are simply put on the stage of the microscope, after the removal of the cover, and examined, first, by low power magnification. More often the sporulation can be seen with the low power magnification, but there is no objection to use of the higher magnification also, after a cover glass has been put on the portion of the plate surface to be examined. After cedar oil has been placed on the cover glass, the immersion lens can also be used. This method saves much time in larger series of examinations. Care has to be taken only that the plates when poured shall be as thin as possible, as thicker layers are apt to show vibrations, which make examination more difficult. By using this method, the influence of some disinfectants on oocysts can be ascertained by adding the disinfectant in a proper concentration to the agar solution.

The eggs of some internal parasites, which were occasionally added to the medium with the feces containing oocysts, showed segmentation and embryonization, when they were kept long enough under observation. Therefore, the plain agar medium might also be used for the study of the eggs of parasites; for such more extended examinations, it might be recommended that the surface of the medium be moistened with some drops of water from time to time.

### SUMMARY

From 0.8 to 1 per cent of agar dissolved in distilled water and poured into Petri dishes constitutes a simple medium for studying the sporulation of coccidial oocysts. The feces containing the oocysts are smeared thinly on the surface of the agar and can be examined directly under the microscope by using the low magnification, the high magnification, or even the oil emersion systems.

# General Review

## THROMBOSIS AND FATAL PULMONARY EMBOLISM

### COMPARISON OF THEIR FREQUENCY IN THE CLINICS OF CENTRAL EUROPE AND NORTH AMERICA, WITH SPECIAL REFERENCE TO INCREASE

SOL ROY ROSENTHAL, M.D.
CHICAGO

In discussing the problems of the increase of thrombosis and pulmonary embolism, one necessarily considers the statistical reports. Such data are at best open to criticism especially as different types of clinical material are reported and as different pathologists have varying interest in these conditions. To avoid as much error as possible, the statistics of each pathologist must be considered as a definite entity. Only the interpretations may be compared and not the actual numerical values.

Hegler, in 1926, was first to call attention to the marked rise of thrombosis in St. Georg Hospital, Hamburg, and since that time there have been many reports relative to this question. The majority of the reports have come from the clinics of Central Europe. Other countries, including the United States, have few, if any, published reports on the subject.

In order to make this review as complete as possible, a questionnaire was sent to leading pathologists in this country. The answers cover representative sections.

Because the reports in this country appear to be different from the European, many of the concepts relative to the pathogenesis of thrombosis and embolism are open to question.

The most direct approach to the interpretation of the reports from the various clinics was found in plotting their values in the form of graphs. Only the percentages were plotted, but these showed such wide variations that a scale had to be used in which corresponding results could be telescoped onto one chart and in which the smaller

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values were not completely overshadowed by the larger ones. The solution of this scale was found in the semilogarithmic four cycle paper, suggested to me by Dr. A. Bachem, biophysicist, at the University of Illinois, College of Medicine. The four cycles are in progression of ten. The smallest value was placed at 0.01, making the largest value 100. From these charts direct values may be read, it being remembered that the coordinate is in a logarithmic scale and represents the percentage of thrombosis or of embolism, while the abscissa is in a linear scale and represents the year.

By maintaining a common scale, the angle of inclination or decline in any given instance can be compared; and by drawing a straight line through each curve, determined by approximately bisecting the values, the mean angle of inclination is obtained. This angle designates the trend of increase or of decrease in thrombosis or in embolism over the years reported. In the charts, the individual curves are represented by an interrupted line, while the average angle of inclination is represented by a continuous line, except where otherwise indicated.

As not all reports lent themselves to plotting in graph form, tables have been constructed to show the percentages of thrombosis and fatal pulmonary embolism of the earliest and latest years embraced in the study. Occasionally other years are mentioned that might influence the report. The reports are derived entirely from postmortem material.

### THE INCIDENCE OF THROMBOSIS IN GENERAL CLINICS OF CENTRAL EUROPE (TABLE 1; CHARTS 1 AND 7A)

The scope of most of the reports covers the years from 1910 to 1930. From the line representing the average angle of inclination, a universal elevation of thrombosis is evident. The lowest increase as deduced from this line is from 4½ to 9½ per cent (Cologne), while the highest increase is from 12 to 30 per cent (Leipzig). To elucidate these interpretations, the following example is cited. In the report of Adolph and Hopman from the Augusta Hospital in Cologne, the percentage of thrombosis in 1912 was 7.5 and in 1927, 9; an increase of 1.5 per cent. When 1926 is considered with a percentage of 10.5 and 1924 with a percentage of 4, the greatest increase is 6½ per cent. The average increase as deduced from the line of inclination is 5 per cent.

That an increase has taken place is claimed universally by the authors reporting, but in some instances there is a slight tendency to return to normal. This can be studied best in chart *7 A*, where is indicated, year by year, the number of clinics denoting tendencies to increase or decrease in thrombosis. In scanning this chart it must be borne in mind that the general trend is toward increase, and that chart *7 A* was constructed from chart 1. Each year is viewed by itself, and the inclination of the respective curves is indicated.

As the World War is considered the most important factor about which the increase in thrombosis and embolism revolves, the study of the corresponding graph is divided into three periods—before the war, from 1910 to 1914; during the war, from 1914 to 1918, and after the war, from 1918 to 1930.

Before the war, as many clinics showed increase as decrease. In 1914 there was a sudden rise in four clinics with a decrease in two.

TABLE 1.—*The Incidence of Thrombosis and Embolism in the General Clinics of Central Europe*

| City and Author | Thrombosis | | Fatal Pulmonary Embolism | |
|---|---|---|---|---|
| | Year | Percentage | Year | Percentage |
| Hamburg: Wertheimer | 1910 | 1.48 | 1910 | 0.44 |
| | 1929 | 11.0 | 1929 | 2.9 |
| Düsseldorf: Schleussing | 1911 | 10.7 | 1911 | 0.4 |
| | 1928 | 17.0 | 1928 | 1.8 |
| Göttingen: Grüber | .... | .... | 1911 | 0.68 |
| | | | 1927 | 3.46 |
| Budapest: Bodin | .... | .... | 1911-1913 | 0.3 |
| | | | 1918-1928 | 1.12 |
| Leipzig: Singer and Morawitz | 1912 | 15.6 | 1912 | 1.5 |
| | 1928 | 29.7 | 1928 | 6.9 |
| Stettin: Auxhausen | 1912 | 6.9 | 1912 | 3.4 |
| | 1928 | 14.0 | 1928 | 8.8 |
| Cologne: Adolph and Hopman | 1912 | 7.5 | 1912 | 1.8 |
| | | | 1919 | 0.8 |
| | 1926 | 10.5 | 1926 | 3.4 |
| | 1927 | 9.0 | 1927 | 1.9 |
| Munich: Oberndorfer | 1912-1914 | 5.0 | 1912-1914 | 2.0 |
| | 1925-1927 | 12.0 | 1925-1927 | 5.0 |
| Hamburg: Hegler | 1913 | 5.0 | 1926 | 50 emboli |
| | 1925 | 10.0 | 1927 | 82 emboli |
| Wiesbaden: Schulz | 1915-1920 | 2.1 | 1915-1920 | 1.0 |
| | 1928 (1st half) | 12.0 | 1928 | 11.3 |
| Freiburg: Kuhn | 1919 | 18.6 | 1919 | 1.61 |
| | 1927 | 24.5 | 1927 | 4.94 |
| Rostock: Höring | .... | .... | 1922 | 1.9 |
| | | | 1927 | 6.8 |
| | Thrombosis and Embolism | | | |
| Munich: Martini and Oppitz | 1924 | 16.4 | | |
| | 1927 | 23.6 | | |

During 1915, 1916 and 1917, there was again a remission, as there were as many reports of decrease as of increase. In 1919 and 1920, the tendency was toward increase, and in the years from 1921 to 1928 it was so without exception. In 1929, a decline set in, but the level was still high, much higher than in the prewar period.

One can deduce, then (charts 1 and 7 *A*), that the actual ascent of the incidence of thrombosis began in 1919, became universal in 1922 and reached its height in 1928. The most pronounced increase was from 1921 to 1927. In 1929, a slight trend for a return to normal is indicated.

### THE INCIDENCE OF FATAL PULMONARY EMBOLISM IN GENERAL CLINICS OF CENTRAL EUROPE (TABLE 1; CHARTS 2 AND 7 B)

Similar to thrombosis, fatal pulmonary embolism has shown a definite increase in the general clinics of Central Europe. The lowest average values were from 1.6 to 2 per cent (Cologne), while the highest values were from 0.44 to 4 per cent (Hamburg, Wertheimer).[1] This increase is not generally as striking as that in thrombosis. The average percentage of increase in thrombosis surpasses that in fatal pulmonary embolism.

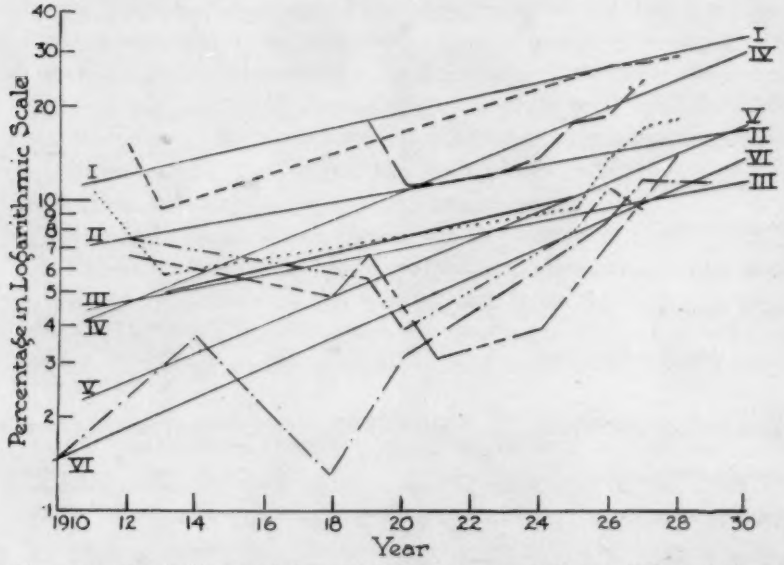


Chart 1.—The incidence of thrombosis in the general clinics of Central Europe: I. Leipzig; II. Düsseldorf; III. Cologne; IV. Freiburg; V. Stettin; VI. (dash and dot); University, Hamburg; VII. (solid line), St. Georg Hospital, Hamburg.

Some authors claim a tendency to return to the prewar number of fatal pulmonary embolisms (Adolph and Hopman, Cologne; Bodin, Budapest).

In considering yearly the inclination of fatal pulmonary embolism (charts 2 and 7 *B*), it appears that before the war there was a decline, while during the war and one year after it there was an increase. In 1920, the increase was definitely established, although not in all cases. In 1923, a decline was found in 36 per cent of the clinics reporting, but the level was above that of the prewar period. Another height was

1. The increase of fatal pulmonary embolism in Wiesbaden was from 1 per cent to 11.3 per cent, but these values did not lend themselves to plotting and are given only in table 1.

reached in 1925; then followed a slight remission to a higher level than in 1923, and finally the highest percentages were reached in the years from 1926 to 1928. After this, many of the clinics (50 per cent) began to show a decline or a stationary level.

The relationship between thrombosis and fatal pulmonary embolism was directly proportional until 1922, when the percentage of thrombosis

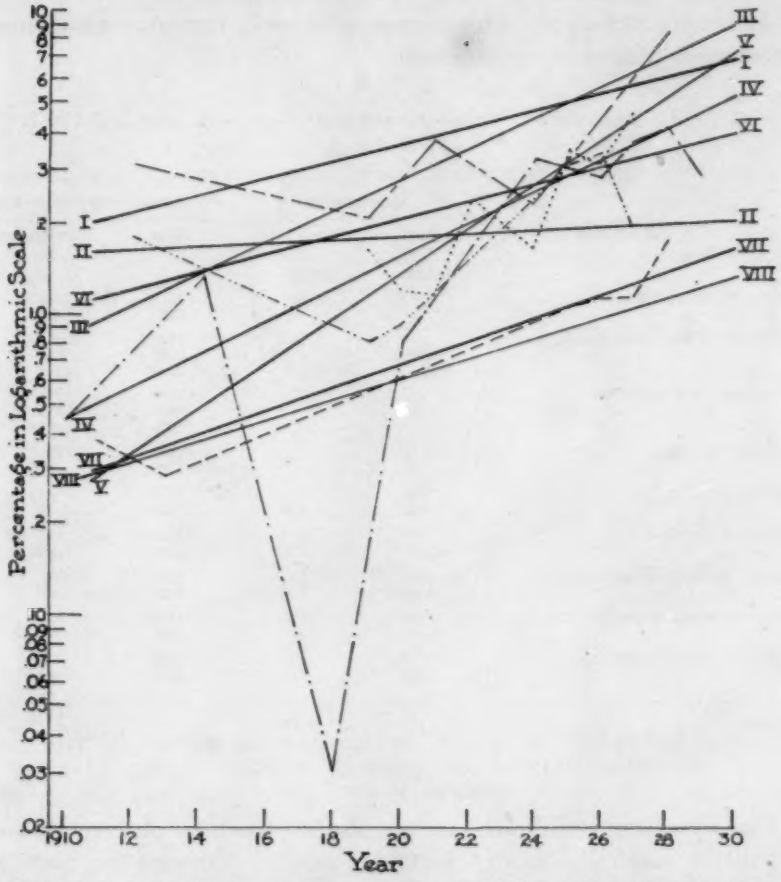


Chart 2.—The incidence of fatal pulmonary embolism in the general clinics of Central Europe: I. Stettin; II. Cologne; III. (no curve), Leipzig; IV. Hamburg; V, Freiburg; VI (no curve), Göttingen; VII, Düsseldorf; VIII (no curve), Budapest.

continued to rise while that of embolism fell. This reversal continued until 1923, when the percentage of embolism rose and continued to do so up to 1925. From this time on, some of the clinics began to show a decline, although the majority still demonstrated an increase. Thrombosis during this entire period was steadily climbing. The acuity of inclination for embolism was also less marked than that for thrombosis.

In summary, the incidence of fatal pulmonary embolism in the general clinics of Central Europe has been on the increase. The rise began with the war, but did not definitely assert itself until 1920. Except for a slight remission, the elevation continued until 1928. The highest percentage was reached during the years from 1926 to 1928, after which 50 per cent of the clinics showed a tendency toward constancy or decrease. The increase in thrombosis was more prolonged than that in pulmonary embolism. The average increase in thrombosis was more pronounced than that in embolism.

TABLE 2.—*The Incidence of Thrombosis and Embolism in the Surgical Clinics of Central Europe*

| City and Author | Thrombosis | | Fatal Pulmonary Embolism | |
|---|---|---|---|---|
| | Year | Percentage | Year | Percentage |
| Hamburg: Hegler | 1913<br>1925 | 0.06<br>0.4 | | |
| Vienna: Stöhr and Kazda | .... | .... | 1915<br>1925 | 0.4<br>1.6 |
| Heidelberg: Sulger and Boszin | .... | .... | 1919<br>1926<br>1928 | 2.9<br>17.4<br>12.3 |
| Göttingen: Geissendorfer | .... | .... | 1919<br>1924<br>1928 | 0.17<br>0.36<br>0.18 |
| Freiburg: Killian | .... | .... | 1919<br>1930 | 0.09<br>0.38 |
| Leipzig: Sarafoff | 1920<br>1929 | 0.33<br>1.07 | 1920<br>1929 | 0.45<br>5.1 |
| Würzburg: Bauer | 1923<br>1928 | 0.27<br>1.15 | 1923<br>1928 | 0.2<br>0.41 |
| Leipzig: Sellheim (gynecology) | 1916<br>1928 | 1.8<br>2.5 | 1914<br>1928 | 0<br>28.0 |
| Leipzig: Sellheim (obstetrics) | 1914<br>1928 | 0.05<br>0.7 | 1914<br>1927 | 0<br>0.15 |
| Tübingen: Mayer (obstetrics) | 1914<br>1929 | 1.9<br>2.0 | 1914<br>1929 | 0.17<br>0.5 |

### THE INCIDENCE OF FATAL PULMONARY EMBOLISM IN THE SURGICAL CLINICS OF CENTRAL EUROPE (TABLE 2; CHARTS 3 AND 7C)

An increase in fatal pulmonary embolism has been observed generally in the surgical clinics of Central Europe. Although the majority of the reports begin with 1919, the authors stated that up to that time the percentage was uniformly low. The average range of increase varied from 0.2 to 0.32 per cent (Göttingen) and from 2 to 16 per cent (Heidelberg). The upper and lower limits are similar to those found in the general clinics, but the average angle of inclination is higher in the surgical clinics.

Judging from the reports, the incidence of fatal pulmonary embolism was rather uniform until 1921. In 1922, a definite rise set in, which with one exception became generalized. But for a slight remission in

1925, the rise continued, reaching its high peaks in 1926 and 1927. In 1928, the tendency was toward a decrease or a standstill, but the level, except in one instance, was higher than that during the first years reported.

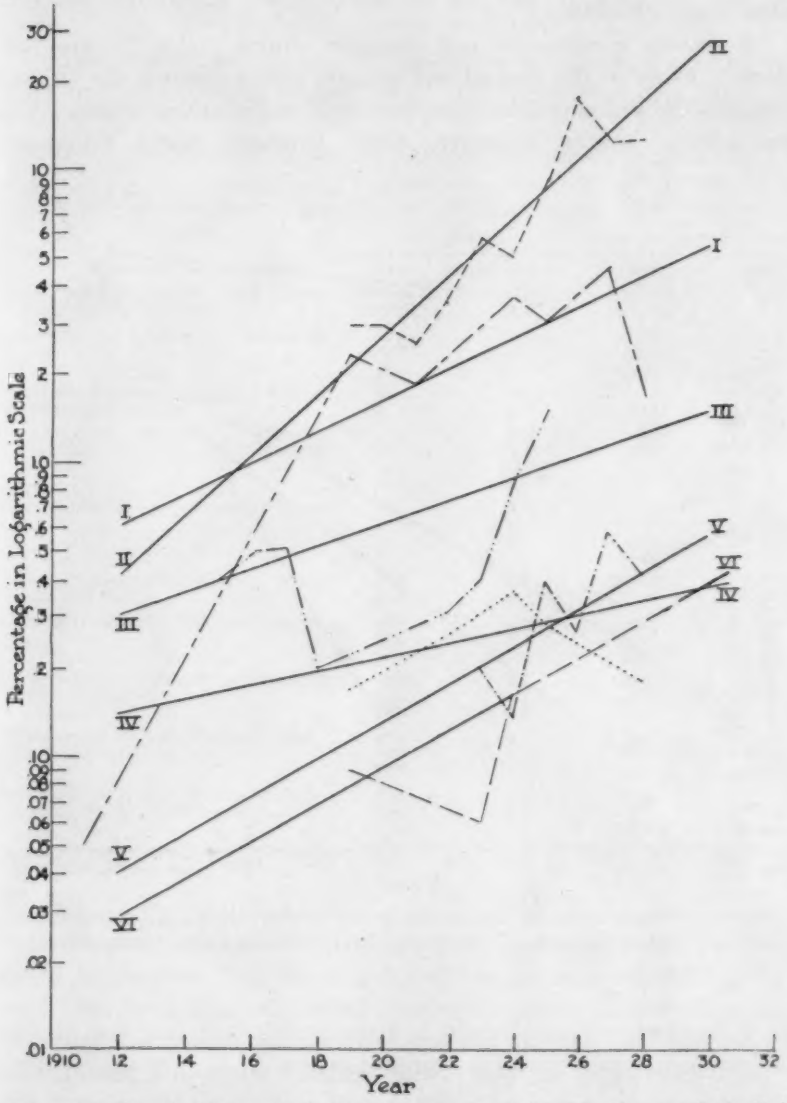


Chart 3.—The incidence of fatal pulmonary embolism in the surgical clinics of Central Europe: I, Budapest; II, Heidelberg; III, Vienna; IV, Göttingen; V, Würzburg; VI, Freiburg.

In summary, the increase in fatal pulmonary embolism in the surgical clinics of Central Europe was pronounced and much more so than in the general clinics. The rise began in 1922 and reached its peak in

1926 and 1927. In 1928, a decline set in, but the level was higher than that given in most previous reports.

Data on thrombosis in the surgical clinics of Central Europe are limited. The four curves cited in chart 4 all show an upward tilt. No comparisons are made.

The purely gynecologic and obstetric clinics (table 2) are few. However, many of the general and surgical clinics mention the increase in thrombosis and embolism in gynecologic and obstetric clinics (Sellheim, Leipzig; Mayer, Tübingen; Kuhn, Freiberg; Bodin, Budapest).

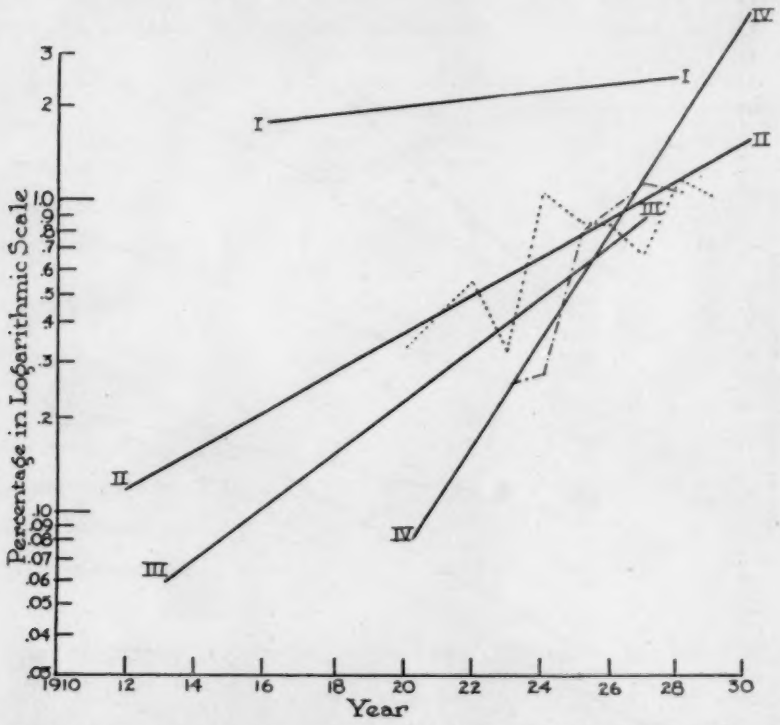


Chart 4.—The incidence of thrombosis in the surgical clinics of Central Europe: I, Leipzig (gynecologic clinic); II, Leipzig; III, Hamburg (St. Georg Hospital); IV, Würzburg.

The gynecologic clinics showed a more pronounced increase of fatal pulmonary embolism than the obstetric clinics.

### THE STATISTICS ON THROMBOSIS AND ON FATAL PULMONARY EMBOLISM IN THE CLINICS OF NORTH AMERICA

These statistics were obtained, save in the case of the Mayo Clinic, by a questionnaire sent to the directors of the pathologic institutes all over the country. An obvious rise of thrombosis and embolism is not manifest.

The data came mainly from general clinics. However, on thrombosis there are two, and on fatal pulmonary embolism three, reports from surgical clinics. Only postmortem material was considered.

### THE INCIDENCE OF THROMBOSIS IN THE CLINICS OF NORTH AMERICA (TABLE 3; CHART 5)

These reports are necessarily considered in groups, according to the span of years covered in each case. Of the five reports dating back

TABLE 3.—*The Incidence of Thrombosis and Embolism in the Clinics of North America*

| Clinic and Author | Thrombosis | | Fatal Pulmonary Embolism | |
|---|---|---|---|---|
| | Year | Percentage | Year | Percentage |
| Presbyterian Hospital, New York: Pappenheimer-Robinson | 1913-1914<br>1930-1931 | 25.7<br>20.9 | 1913-1914<br>1930-1931 | 11.1<br>6.2 |
| University of Minnesota: McCartney | .... | .... | 1913<br>1929<br>1930 | 1.0<br>0.7<br>1.7 |
| Stanford University Medical School: Ophüls and Dobson | 1913<br>1931 | 6.7<br>23.0 | 1913<br>1931 | 1.0<br>1.5 |
| Northwestern University, affiliated hospitals: Simonds and Dyrenforth | 1914<br>1916<br>1920<br>1930 | 10.0<br>28.0<br>14.0<br>20.8 | 1918<br>1930 | 1.7<br>1.5 |
| Los Angeles General Hospital: Evans | 1917<br>1929<br>1931 | 1.5<br>4.5<br>6.7 | 1917<br>1926<br>1930<br>1931 | 0<br>0.2<br>0.1<br>0.3 |
| Toronto General Hospital: Koltz, Belt and Smith | 1926<br>1930 | 18.0<br>16.4 | 1926-1930 | 3.1 |
| Cincinnati General Hospital: Austin | 1926<br>1930<br>1931 (1st half) | 0.23<br>2.1<br>4.2 | 1920<br>1930<br>1931 | 2.1<br>1.0<br>2.4 |
| Cook County Hospital, Chicago: Jaffé, Rosenthal | 1929<br>1930<br>1931 | 13.4<br>10.7<br>6.0 | 1929<br>1930<br>1931 | 0.2<br>0<br>0.33 |
| Presbyterian Hospital, surgical clinic, New York: Palmer | 1913<br>1928<br>1930 | 0<br>0.77<br>1.27 | 1913<br>1928<br>1930 | 0.05<br>0.66<br>0.4 |
| Stanford University Medical School, surgical clinic: Ophüls and Dobson | 1913<br>1931 | 1.0<br>0.2 | 1913<br>1917<br>1931 | 0<br>1.5<br>0.5 |
| Mayo Clinic, surgical dept., Rochester, Minn.: Hendersen, Walters | .... | .... | 1917-1927<br>1926-1930 | 0.34<br>0.09 |

to the prewar period (table 3), that for the general clinic of the Presbyterian Hospital in New York and that for the surgical clinic of Stanford University Medical School show a decrease, while three show an increase: Northwestern University hospital affiliates, the surgical clinic of Stanford University Medical School and the surgical clinic of the Presbyterian Hospital, New York. The Los Angeles General Hospital, reporting from 1917, shows an increase. Of the three clinics reporting from 1926 on, the Cincinnati General Hospital shows an increase and the Toronto General Hospital and the Cook County Hospital, Chicago, a decrease.

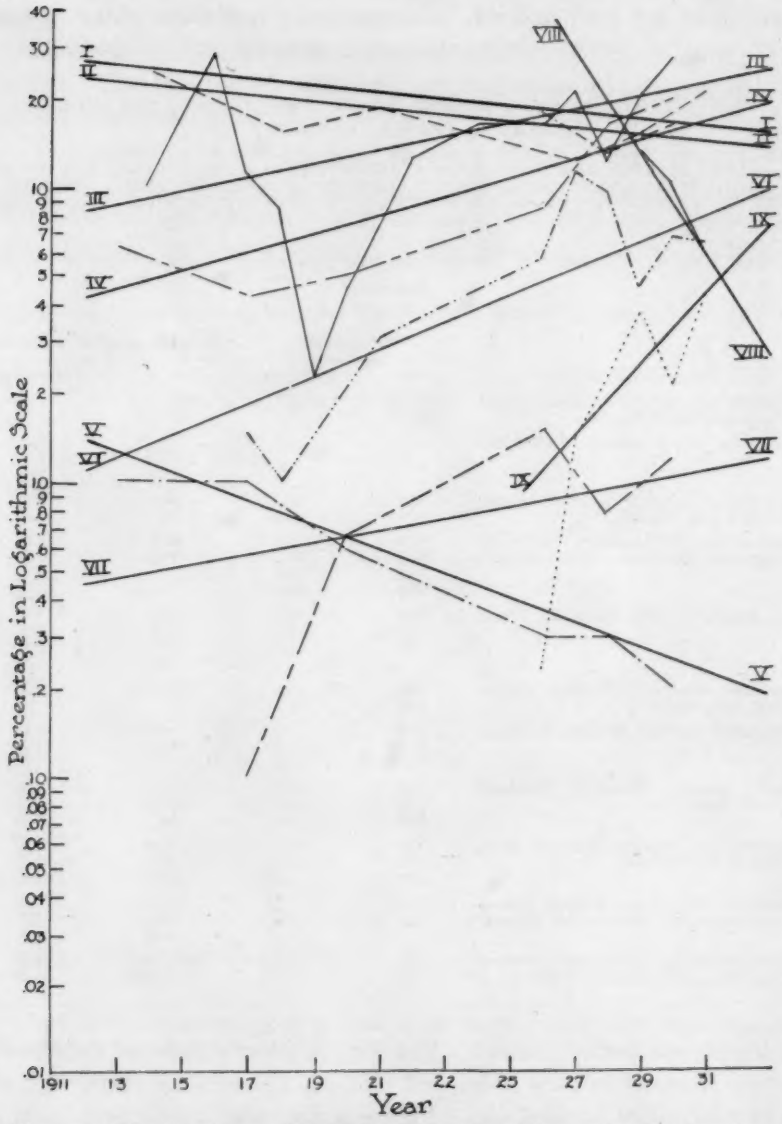


Chart 5.—The incidence of thrombosis in the clinics of North America: I, Toronto General Hospital; II, Presbyterian Hospital, general clinic, New York; III, Northwestern University and affiliated hospitals, Chicago; IV, Stanford University, medical clinic; V, Stanford University, surgical clinic; VI, Los Angeles General Hospital; VII, Presbyterian Hospital, surgical clinic, New York; VIII, Cook County Hospital; IX, Cincinnati General Hospital.

Taking these reports together, one may deduce that concerning the period between 1914 and 1931, opinion has been divided as to increase in thrombosis. It is impossible thus to arrive at any definite conclusions. Because the statistics for fatal pulmonary embolism are more complete, and because, generally speaking, the incidence of thrombosis and that of embolism run parallel, further deductions will be offered on pulmonary embolism.

### THE INCIDENCE OF FATAL PULMONARY EMBOLISM IN THE CLINICS OF NORTH AMERICA (TABLE 3; CHART 6)

These reports lend themselves more appropriately for comparison with those of Central Europe. Their scope in the majority of instances embraces the prewar period (1913 to 1931) and, with the exception of one instance, the results show a decrease, no change or a slight increase.

Specifically, the clinic showing an increase is the surgical clinic in the Presbyterian Hospital, New York, from 0.09 to 0.8 per cent; but to counteract this rise, the other surgical clinics showed a fall, from 0.34 to 0.09 per cent, Mayo Clinic, and from 1.5 to 0.5 per cent, Stanford University Medical School. The remaining eight reports give no indication of an increase in deaths from pulmonary embolism, but indicate rather a decrease.

In summary, there has been no increase in fatal pulmonary embolism in the clinics of North America. Because of the usual parallelism between thrombosis and embolism, and because the opinions as to the incidence of thrombosis are divided and incomplete, one may deduce that there has been no increase in thrombosis.

In comparing the reports of the Central European and the North American clinics, caution is exercised because of the discrepancy in the number of clinics reporting and in the number of years included in the reports. However, it must be borne in mind that the European statistics have been instigated by the alarm caused by an apparent increase in thrombosis and pulmonary embolism. All of these reports have been published, while the North American statistics are the result of a questionnaire sent out by me. In other words, there has been no noticeable rise in thrombosis and embolism in this country to warrant publication. To bear this out, the North American reports, when complete, show a tendency toward decrease rather than increase. This is especially true in regard to pulmonary embolism, about which this paper is most concerned.

In view of these circumstances, many factors held responsible for the pathogenesis of thrombosis and embolism may be excluded.

The European authors point at old age, cardiac and vascular changes, modern methods of therapy (especially intravenous), postwar inflation (1919 to 1924), surgical procedures (including anesthetics), nutrition,

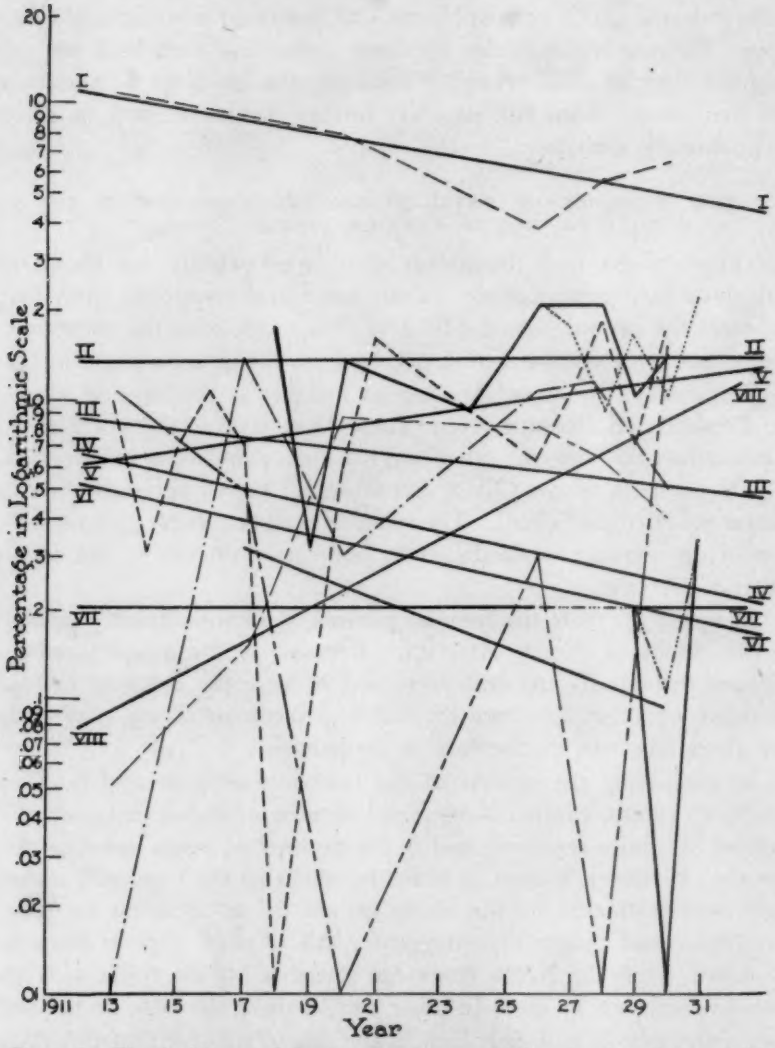


Chart 6.—The incidence of fatal pulmonary embolism in the clinics of North America: I, Presbyterian Hospital, general clinic, New York; II, Northwestern University and affiliated hospitals, Chicago; III, Stanford University, surgical clinic; IV, Stanford University, medical clinic; V, University of Minnesota; VI, Cook County Hospital; VII, Los Angeles General Hospital; VIII (long dash-short dash), Presbyterian Hospital, surgical clinic, New York; VIII (solid line), Mayo Clinic, Rochester, Minn.

the influenza epidemic and changes of the weather, as influencing the rise of thrombosis and pulmonary embolism. These conditions will be considered later and compared with the conditions in North America, especially at the Cook County Hospital, Chicago, in which 2,500 consecutive autopsies have been reviewed.

### THE RELATIONSHIP OF AGE TO THE RISE OF THROMBOSIS AND PULMONARY EMBOLISM

Without exception, the European authors have found the greatest number and percentage of cases of thrombosis and fatal pulmonary embolism in persons between the ages of 40 and 70 years (Kuhn, Klinke, Singer and Morawitz, Oberndorfer, Höring, Adolph and Hopman, Sellheim, Geissendorfer, Killian, Grüber, Hutter and Urban, Schulz, Bauer, Qure). The greatest number of cases occurred in persons between the ages of 40 and 50 years, while the highest percentage was that of cases occurring in persons between 60 and 70 years of age.

In this country, the average age for thrombosis and pulmonary embolism, as found in the Toronto General Hospital, Canada, in the Northwestern University affiliated hospitals, Chicago, and in the Stanford University Medical School, San Francisco, was about 50 years. This does not include the age incidence with the highest percentage. At the Cook County Hospital, Chicago, the greatest number of cases occurred in persons between 41 and 50 years of age, while the highest percentage was that of cases in persons between 61 and 70 years of age.

In summary, the age incidence for thrombosis and fatal pulmonary embolism in Central Europe is similar to that in this country (where reports are available). That this factor alone is responsible for an increase, thus becomes doubtful.

### THE RELATIONSHIP OF CARDIAC AND VASCULAR CHANGES TO THE RISE OF THROMBOSIS AND PULMONARY EMBOLISM

Observations directed to the circulatory system reveal that changes in the heart and, to a lesser extent, in the blood vessels are in the majority of instances associated with thrombosis and embolism. The Central European reports designate this relationship in from 51.7 per cent (Axhausen) to 95 per cent (Bauer) of the cases. It is of interest to note that not only general clinics proclaim this as a factor of utmost importance (Höring, Fahr, Oberndorfer, Martini and Oppitz, Kahn, Klinke, Singer and Morawitz, Schleussing, Schulz, Bodin, Adolph and Hopman, Axhausen, Wertheimer) but also surgical clinics (Nippe, Sellheim, Sarafoff and Bauer). Bauer pointed out that although only 20 per cent of the patients who died of pulmonary embolism at the Würz-

burg surgical clinic presented circulatory disturbances clinically, 95 per cent of them showed myocardial and vascular changes on postmortem examination.

Thrombosis and pulmonary embolism were associated with cardiac and vascular lesions in over 80 per cent of the cases at the Cook County Hospital and in 52 per cent of the cases at the Stanford University Medical School.

In summary, cardiac and vascular conditions play an important rôle in thrombosis and embolism, both in Central Europe and in this country (Hendersen, Walters, Polak, Rosenthal, Ophüls and Dobson).

### THE RELATIONSHIP OF SURGICAL PROCEDURES TO THE RISE OF THROMBOSIS AND EMBOLISM

Although some authors report a greater increase of thrombosis and embolism in the medical clinics (Axhausen, Kuhn, Klinke, Schleussing, in 1929), the majority of authors state that the rise has been more pronounced in the surgical clinics (Geissendorfer, Bodin, Schleussing [1924-1927], Höring, Bauer, Hueck, Wahlig, Sulger and Boszin, Killian, Hegler, Stöhr and Kazda). This can best be seen by comparing charts 2 and 3

Of the surgical procedures, laparotomy is more frequently associated with thrombosis and embolism (Geissendorfer, Bodin, Höring, Bauer, Hueck, Kuhn, Detering, Patey, Petren, Ducuing, Miller and Rogers, and McCartney). The usual order of frequency of thrombosis and embolism in relation to the organs is as follows: prostate, stomach, gallbladder, appendix, hernia (Höring, Geissendorfer, Bauer). It is well to remember in this regard that the associated lesions in prostatic hypertrophy are, as a rule, hypertrophy of the heart with dilatation, and urinary infection.

Because of the frequency of thrombosis and embolism following surgical procedures, the nature of the blood, preoperative and postoperative, has been studied in the search for an explanation. The results of these researches will be discussed later. It is sufficient to mention here that changes in the bleeding and clotting time, in the concentration and sedimentation and in carbon dioxide, lipoid and calcium content have all been given as factors influencing the formation of thrombi. Yet these factors do not account for the increase in thrombosis, as surgery is practiced in this country on a huge scale, while the incidence of thrombosis and fatal lung embolism has not increased.

In summary, the greatest increase in thrombosis and pulmonary embolism in the Central European clinics was found to follow surgical procedures. But neither this fact nor postoperative changes in the

blood explain the increased incidence, for surgery is practiced in this country to about the same extent as in Central Europe.

### THE RELATIONSHIP OF MEDICATION TO THE RISE OF THROMBOSIS AND EMBOLISM

The modern methods of intravenous therapy have been considered to play an important rôle in the high incidence of thrombosis and embolism (von Linhard, Oehler, Fahr, Hegler, Reye, Martini and Oppitz, Kuhn). These authors agree with Martini and Oppitz that although a large percentage follows intravenous injections (38 per cent) a higher percentage follows intravenous therapy in cases of heart disease (81 per cent).

On the contrary there are as many reports showing that intravenous therapy has played but a slight rôle in the increase of thrombosis (Adolph and Hopman, Bodin, Schulz, Wahlig, Schleussing, Oberndorfer, Singer and Morawitz, Hueck, Höring). Some of these authors have gone so far as to say that the greatest increase in thrombosis and embolism has occurred in patients who did not receive intravenous medication (Adolph and Hopman, Hueck). Oberndorfer and Höring have stated that the modern intensive cardiac therapy has been a greater factor in the increase in thrombosis than intravenous injection.

It cannot be denied that intravenous medication of intensive cardiac therapy applied to older patients with cardiac lesions predisposes to the formation of thrombi. But the factor of therapy alone cannot be held responsible for the rise in thrombosis and embolism, as these newer methods of medication are used extensively in this country and yet no increase in thrombosis and embolism has been noted.

There are occasional reports of pulmonary embolism following intravenous injections of bismuth (Garcia, Joulia, Petges and Joulia), arsenic (Burn and Bromberg) and corrosive solutions used to occlude varicose veins (Silverman). These instances are rare. Silverman found for corrosive solutions an incidence of less than 0.015 per cent. This does not consider the thousands of clinics using this form of therapy, in which no pulmonary embolism has occurred.

In summary, intravenous injections and intensive cardiac therapy per se have not been responsible for the increase in thrombosis and embolism.

### THE RELATIONSHIP OF NUTRITION TO THE RISE OF THROMBOSIS AND PULMONARY EMBOLISM

Because fatal pulmonary embolism was found more frequently in well nourished to obese persons, it was deduced that the improvement of nutrition in the postwar inflation period might bear a direct relation-

ship to it (Deider, Kuhn, Schulz, Wahlig, Bauer). That pulmonary embolism frequently occurs in obese persons has been noted also in this country (Hendersen, Snell, Polak and Mazzola, Rosenthal). But in a previous report, I have shown that, in the well nourished, 84 per cent of the cases of thrombosis and embolism were associated with cardiac and vascular changes as compared with 64 per cent in the undernourished. Of the four fatal cases of pulmonary embolism in 2,500 autopsies at the Cook County Hospital, all were in obese women, with hypertrophic and dilated hearts.

The augmentation of cardiac and vascular diseases is thus of greater importance in the formation of thrombi and emboli than the betterment of nutrition. The foods of the Central European peoples during the inflation period, high in carbohydrate and low in vitamins, must have had much bearing on the increase in heart disease, for, as has been shown by Ohmori, a deficiency of vitamin B leads to dilation of the heart.

In summary, pulmonary embolism is most common in obese persons, but the obesity is probably of less significance than the cardiac and vascular changes.

### THE RELATIONSHIP OF THE INFLUENZA EPIDEMIC TO THE RISE OF THROMBOSIS AND EMBOLISM

The epidemic of influenza that followed the war is considered by some (Franke) to have influenced the increase in thrombosis and embolism. Franke stated that the infection directly affected the endothelium and led to thrombus formation. Bodin and Kuhn could find no relationship between the epidemic and the increase in thrombosis and embolism. Cajigal reported only one case of death from pulmonary embolism in 100 postmortem examinations during the influenza epidemic. This may be taken to mean that there was not an increase in pulmonary embolism in Barcelona during 1919. A similar observation was made by Nagajo of Tokyo.

In the United States, the epidemic was widespread and intense. Yet there has been no increase in thrombosis and embolism.

In summary, the influenza epidemic played no rôle in the increase of thrombosis and embolism.

### THE RELATIONSHIP OF WEATHER CONDITIONS TO THE RISE OF THROMBOSIS AND EMBOLISM

Opposite views are held regarding the effect of weather conditions on thrombosis and embolism. Killian of Freiburg, in analyzing the weather charts of that locality, pointed out that during July and August, the dry south winds favored the formation of thrombi because

of the increased perspiration and evaporation. He found most cases of thrombosis and embolism in October, July and August and the fewest in June and September. The recent increase of southerly winds, Killian felt, partly influenced the rise of thrombosis and embolism.

On the contrary, Fritzsche, Klinke, Geissendorfer, Bauer and Sarafoff showed that the most cases of thrombosis occurred during the wet, stormy and cold weather. Bauer explained this by the fact that

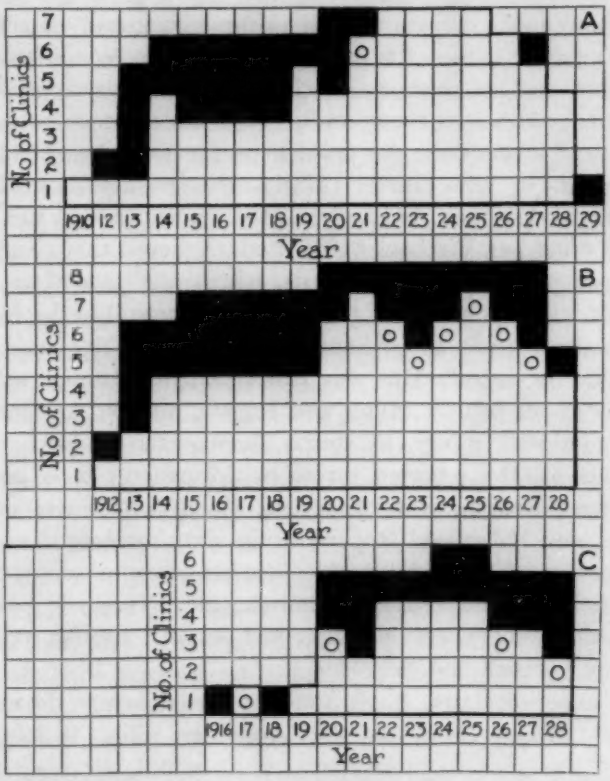


Chart 7.—The relationship between the increase and decrease of (*A*) thrombosis in the general clinics, (*B*) fatal pulmonary embolism in the general clinics and (*C*) fatal pulmonary embolism in the surgical clinics, of Central Europe. The white square indicates increase; the solid black square, decrease, and a circle, no change.

there are twice as many illnesses in the winter as in the summer. Fritzsche's stand was that during wet and stormy weather, the increase of electric charge of the air acts on the autonomic nervous system and influences the vascular mechanism. This promotes stasis and leads to thrombosis. The same author also stated that the present mode of living, especially in the early postwar period, resulted in instability of the autonomic nervous system.

The reports from this country are derived from all quarters, moist, dry, hot and cold, but there has been no increase in thrombosis and embolism. As to the present mode of living, in this country, it probably surpasses in eccentricity and momentum that of Central Europe.

In summary, weather conditions and changes in the mode of living do not account for the elevation of thrombosis and embolism.

## COMMENT

In attempting to explain the rise in thrombosis and embolism in the Central European clinics, the pathogenesis of these conditions has been studied, and modern methods of chemical and physical analysis have been applied. Although these studies have added much to the present conception of thrombosis, the problem is far from being solved. The earlier theories of John Hunter (1794), who spoke of vascular changes as a result of infection, of Andral (1842), who added the factor of stasis and finally of Virchow (1885), who believed that changes in the blood, vascular alterations and stasis, whether associated or not associated with infection, may lead to thrombosis, are still in the foreground.

Stasis alone, from an experimental standpoint, does not terminate in thrombus formation. This was first shown by Baumgarten in 1877, and has been verified by Miller and Rogers, and by Armentrout. On adding endothelial injury to stasis, Baumgarten and more recently Armentrout (1931) reported thrombus formation. It is questionable whether true thrombi were produced. More likely, mere coagulation took place, for Miller and Rogers, using sixty-three cats, were unable to produce true thrombi by double ligation of veins with scarring of the endothelium, interposition of muscle, etc. They did produce one thrombus at a site where infection had set in. Similar results were obtained by Dietrich and Schröder.

Thus, experimentally, stasis and endothelial injury do not lead to thrombosis, although both may play important rôles. It follows, then, that blood changes are prerequisite, and, indeed, all modern writers agree in that regard. As to the nature of these changes, there is much disagreement. The increased incidence of surgical procedures has been offered as influencing the rise of thrombosis and embolism. Extensive studies of the blood have established increased blood protein through absorption from surgical wounds (Zschau, Stöhr and Kazda); increased blood calcium, carbon dioxide content, sedimentation and concentration (Qure); increased fibrinogen and globulin, which rob the red blood corpuscles and platelets of their electrical charge and promote agglutination (von Seeman, Stuber and Lang); shortening of the clotting and bleeding time (Sulger, Boszin); colloidal chemical and physical changes in the blood (Höring, Allen, Wildegans), and increase in

blood platelets from the eighth to the eleventh day postoperatively, when the majority of thrombi are formed (Hueck, Miller).

Undoubtedly many of these factors may influence thrombosis, but they are not necessarily related to operative procedures. After injections of sugar solutions or in carcinoma, an increase in the globulin and fibrinogen content of the blood has been demonstrated (Stuber and Lang, Wildegans); an increase in platelets and blood protein has been found following a diet high in protein (Milles); clotting time is decreased in infection (Jürgens); carbon dioxide content of the blood is increased in infections, which leads to a decrease in the platelet charge (Prima); calcium and cholesterol are increased in atherosclerosis (Gechtman and Slauskayu). Finally, surgical procedures have also increased to a great extent in this country, with no corresponding increase in thrombosis and embolism.

Thus one may conclude that the changes in the blood observed postoperatively may not be the result of surgical procedures, and that the increase in surgical operations does not account for the increase in thrombosis and embolism.

Dietrich championed the importance of infection in thrombosis. He agreed with Klemensiewicz that a thin layer of a homogeneous substance forms on the endothelium at the site of the thrombus. This, he explained, is the result of a sensitization of the endothelium, after which there is a direct reaction between endothelium and blood to form the thrombus. All these factors are directly influenced by chronic infections; stasis merely acts in localizing the clot. Experimentally, sensitization of an organism has resulted in foci of endothelial proliferation. Actual thrombosis has been produced when suppuration was introduced with stasis (Dietrich and Schröder, Miller and Rogers). Jürgens, by the use of a capillary thrombometer, found a decrease in clotting time in infections.

Suppuration and infection, then, alter the blood and in some instances also the endothelium. The most important rôle of the latter condition is, however, its effect on the blood generally, for in the material at the Cook County Hospital, it was found that generalized infections and remote suppurations by far outnumbered proximal suppurations in relation to thrombosis.

Agreeing that infections and suppurations play a part in thrombus formation, what bearing has that on the increase in thrombosis and embolism? With the first report of an increase in the latter conditions, Hegler emphasized the concomitant increase in diseases generally—pernicious anemia, chlorosis, endocarditis, abscess of the lung, grippe and bronchopneumonia. An increase in the incidence of infectious processes has also been reported by Schleussing and Klinke.

In this country there have been no reports of any increase in infections or in thrombosis and embolism. It seems probable, then, that a higher incidence of infections and suppurations in Central Europe may account partly for the increase in thrombosis and embolism.

As has been stated, the European authors and a survey at the Cook County Hospital have shown that cardiac and vascular changes are frequently associated with thrombosis and embolism. Stasis in heart failure and endothelial injury alone do not account for thrombus formation. There must exist changes in the blood. These changes may result from increased destructive processes during the descending stage of life (40 years onward, Aschoff), increased carbon dioxide content of the blood in myocardial insufficiency (Friedemann) or increased calcium and cholesterol in atherosclerosis (Gechtman and Slauskayu).

That there has been an increase in cardiac and vascular diseases following the war is widely accepted in Central Europe; much more so than in infections and suppurations (Wertheimer, Sellheim, Höring, Oberndorfer, Fahr, Bauer, Klinke, Kuhn, Martini and Oppitz). The explanations offered for this increase are: weakened condition of the heart as a result of hunger and nervous irritability which became manifest long after the war (Wertheimer, Sellheim), changes in the autonomic nervous system that accelerated cardiac and vascular changes (Fritzsche) and changes in the vascular system and the myocardium from epidemics affecting these systems (diphtheria, 1915 to 1918, meningitis, 1924, Klinke).

Thrombosis and embolism began to increase in 1919; the increase advanced in 1922 and extended to the period from 1926 to 1928. These years correspond fairly well to the postwar inflation period that began in 1919. During this period, as stated, the diet of the people in Central Europe consisted mainly of carbohydrates with little vitamin-containing food. This was a result of abandonment of the strict distribution of food. The injurious effects of deficiency in vitamins are well known. The lack of vitamin B causes dilatation of the cardiac chambers (Ohmori). This lack, then, should be included among the factors responsible for the increase in cardiac and vascular disease.

The rise of circulatory disturbances and that of thrombosis and embolism run almost parallel in the clinics of Central Europe. It is the former factor, then, which may be largely responsible for the increase in thrombosis and embolism.

## SUMMARY

A survey of the literature discloses an increase in the incidence of thrombosis and pulmonary embolism in the clinics of Central Europe.

This rise was prevalent in the general, as well as the surgical, clinics, although more marked in the latter.

As a rule, the actual ascent began in 1919, became universal in 1922 and reached its height in 1928. Later than 1928 a decline became manifest.

The increase in thrombosis was more prolonged than that in pulmonary embolism.

The cause of the increase in thrombosis and embolism was largely the rise of cardiac and vascular disease and to a less extent the increase in infections and suppurative diseases.

The accentuation of cardiac and vascular diseases is explained by the hunger, nervous irritability and lack of vitamins that were especially manifest during the period of inflation (1919 to 1924) in Central Europe.

Reports from clinics in the United States and Canada fail to show an elevation in the incidence of thrombosis and pulmonary embolism.

The conflict in the reports from this country and from Europe makes it necessary to question many of the concepts relative to the pathogenesis of thrombosis and embolism. The factors that can be discounted are: operative procedures, weather conditions, the influenza epidemic, intravenous therapy and extensive heart therapy.

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# Notes and News

**University Notes, Promotions, Resignations, Appointments, Deaths, etc.**—Graham Lusk, professor of physiology at Cornell University Medical College and scientific director of the Russell Sage Institute of Pathology, died on July 19, 1932, at the age of 66.

Frank P. Underhill, professor of pharmacology and toxicology in the school of medicine of Yale University, died on June 28, 1932, at the age of 55. He was professor of pathologic chemistry in Yale University from 1913 to 1918.

Bernhard Bang, professor of pathology and therapy in the Royal Veterinary and Agricultural College in Copenhagen, Denmark, died on June 22, 1932, at 83 years of age. Educated in human medicine, he became a leader in veterinary medicine. He devised a method, known as Bang's method, for the eradication of bovine tuberculosis, and isolated the bacillus of infectious abortion (Bang's bacillus).

According to *Science*, members of the staff of the Rockefeller Institute for Medical Research have accepted appointments as follows: Phillip Levine, instructor of pathology and bacteriology in the University of Wisconsin; J. Lionel Alloway, assistant professor of bacteriology in Cornell University Medical College; Ralph Knutti, resident pathologist at the Strong Memorial Hospital, Rochester, N. Y., and Douglas Sprunt, assistant professor of pathology in the medical school of Duke University.

**Society News.**—The Ohio Society of Clinical and Laboratory Diagnosis has appointed Jonathan Forman, Columbus, O., as chairman of a committee to work with a committee from the Ohio Embalmers' Association in the interest of securing more autopsies under proper conditions throughout the state of Ohio.

The International Association for the Study of Paradentosis has been organized. The first annual meeting was held at the University of Zurich on Aug. 7, 1932. Dr. Hermann Becks, Hooper Foundation for Medical Research, Second and Parnassus avenues, San Francisco, is the American representative.

**Study of Whooping Cough.**—A grant of $25,000 from the Rockefeller Foundation to finance a four-year study of whooping cough has been announced by Western Reserve University. Gerald S. Shibley, associate professor of medicine in the medical school, will conduct the investigation, which will cover etiology, prevention, diagnosis and treatment. Cases appearing in the dispensary of Lakeside Hospital and in the community will furnish the material for observation. James Angus Doull, professor of hygiene and public health, will cooperate in the study.

**Graduate Fortnight of the New York Academy of Medicine.**—The next Fortnight, October 17 to 28 inclusive, 1932, will be devoted to the discussion of tumors. At the same time an exhibit of anatomic specimens will be set up in the Academy building. Further information may be obtained from the Academy, 2 East 103d Street, New York.

# Abstracts from Current Literature

## Experimental Pathology and Pathologic Physiology

Osteogenesis Imperfecta Associated with Lesions of the Parathyroid Glands. T. C. Wyatt and T. H. McEachern, Am. J. Dis. Child. **43**:403, 1932.

In the case described there were marked congenital dysplasia of bone and unusual vascularity of the parathyroid glands with a relatively small amount of parenchymal tissue. A brief review of osteogenesis imperfecta and of the relation of the parathyroid glands to disease of bone is given. The possibility is suggested that so-called osteogenesis imperfecta may sometimes be based, in part, on a congenital parathyroid disturbance rather than on faulty mesoblastic differentiation.

Authors' Summary.

Effect of Cabbage Feeding on the Morphology of the Thyroid of Rabbits. I. T. Zeckwer, Am. J. Path. **8**:235, 1932.

Feeding winter cabbage in the early part of 1931 to seventeen rabbits for periods up to one hundred and fourteen days produced hyperplasia of the thyroid gland, but only in two instances did it result in an enlargement more than twice the normal weight. The microscopic changes of hyperplasia were more conspicuous than the gross enlargement. Under the conditions of these experiments, the feeding seemed to favor a high incidence of intercurrent infections. The data, in so far as a small series of experiments permits conclusions, support the view that there is annual variation in the goiterogenic agent of cabbage.

Author's Summary.

The Dynamic Bronchial Tree. Charles C. Macklin, Am. Rev. Tuberc. **25**:393, 1932.

The lop-sided inspiratory enlargement of the pleural cavity makes it necessary for the lung, in inspiration, to shift itself so as to occupy the new space, and thus one finds the hilus, in this phase, moving downward, forward and outward, and, in expiration, reversely. This oscillation is marked in forcible breathing, and is necessary to the proper ventilation of the part of the lung lying above and behind the hilus. Much depends on the physical condition of the root, which normally is flexible, allowing this adaptational movement to take place freely. When, however, the root is stiffened from disease processes, which may originate in early life, the movement is hampered or abolished, and then the subapical region, in particular, suffers. Thus it is suggested that impairment of the flexibility of the root may have a good deal to do with the site of election of a tuberculous process. Diagrams are used to make clear the points brought out, and a plea is made for concerted attention of clinicians to the lung root, to the end that its physiology and pathology may be better understood.

C. C. Macklin.

Effects of Cinchophen in Rats. Herbert S. Reichle, Arch. Int. Med. **49**:215, 1932.

Subcutaneous administration of cinchophen in single doses of 1 Gm. per kilogram of body weight killed rats within twenty-four hours. Continued parenteral administration of smaller doses (0.2 Gm. per kilogram) did not cause death, but after the last two injections the rats displayed symptoms that may possibly be

regarded as expressions of hypersensitiveness. Feeding of cinchophen in doses of approximately 20 mg. a day to rats when the livers had been depleted of glycogen by starvation or injured by chloroform did not induce cirrhosis. On postmortem examination, no characteristic changes in the histologic appearance of the organs were found. A review of the histories of cases of reaction to cinchophen suggests that its cause may be found either in natural or in developed hypersensitiveness.

AUTHOR'S SUMMARY.

EXPERIMENTAL VENTRICULAR DISTORTION AND CONVULSIONS IN THE CAT. S. B. WORTIS, Arch. Neurol. & Psychiat. **27**:776, 1932.

Aseptic laceration of the brain without removal of the products of trauma, in the cat, results in ventricular distortion due to meningocerebral adhesions and contracting cerebral cicatrix. Head trauma resulting in the escape of blood into the cerebrospinal fluid often gives rise to mild bilateral ventricular dilatation in the absence of grossly demonstrable meningocerebral adhesions or a cerebral scar. Aseptic laceration of the brain and head trauma resulting in fracture of the skull increase the animal's sensitiveness to a standard convulsant over the period of observation.

AUTHOR'S SUMMARY.

TRAUMATIC SUBDURAL HEMATOMA. W. J. GARDNER, Arch. Neurol. & Psychiat. **27**:847, 1932.

In the subdural hematoma there occurs a gradual increase in size. This progression is due to environmental conditions, particularly to inadequacy of lymphatic drainage from the mesothelium-lined subdural space. The increase is due to an accession of tissue fluid, particularly spinal fluid, which is drawn into the hemorrhagic cyst through the semipermeable arachnoid membrane and the adjacent wall of the cyst by the osmotic tension of the blood proteins contained in the cyst. It is difficult, if not impossible, to reproduce in the dog the clinical picture of subdural hematoma.

AUTHOR'S SUMMARY.

THE MONRO-KELLIE HYPOTHESIS OF CONSTANT INTRACRANIAL CONTENT. L. H. WEED and L. B. FLEXNER, Bull. Johns Hopkins Hosp. **50**:196, 1932.

Two series of experiments on animals were carried out, in which records were kept of the pressure of the cerebrospinal fluid, of the sagittal venous pressure and of the carotid arterial pressure. In the first series, the cranial dura was widely exposed to the atmosphere, while in the second series the vertebral arches were removed throughout the thoracic and lumbar regions, thus exposing a large extent of the spinal cord directly to atmospheric pressure. In the animal with the cranial dura exposed, the alteration in the pressure of the cerebrospinal fluid, on abrupt tilting from the horizontal to the vertical tail-down position, was considerably less than the alteration of pressure in this fluid in an intact animal on such a tilt. When the animal with cranial dura exposed was tilted from the horizontal to the vertical head-down position, the alteration of pressure was of exactly the same magnitude as in the intact animal. In the series with the vertebral canal opened, the changes in pressure in the cerebrospinal fluid, on tilting from the horizontal to the vertical tail-down position, were of exactly the same magnitude as in the intact animal. On tilting from the horizontal to the vertical head-down position, the changes in pressure were considerably greater than in the intact animal. These experiments are taken to indicate that the intact character of the vertebral and cranial bony system is essential for the adequate protection of the central nervous system against alterations in pressure in the cerebrospinal fluid, on tilting from the horizontal to the vertical position.

AUTHORS' SUMMARY.

SPONTANEOUS SUBARACHNOID HEMORRHAGE. W. R. OHLER and D. HURWITZ, J. A. M. A. **98**:1856, 1932.

Spontaneous subarachnoid hemorrhage, which occurs more frequently than is generally understood, comes on suddenly, usually with headache, occasionally with vomiting, dizziness, stupor or coma, and rarely with convulsions. Stiff neck, Kernig's sign, fever and slight leukocytosis may lead to confusion of this condition with meningitis. Hypertension is present frequently.

PERMEABILITY OF THE SKIN VESSELS. P. D. MCMASTER and S. HUDACK, J. Exper. Med. **55**:417 and 431, 1932.

The gradient of permeability that exists along the cutaneous capillaries and venules is accentuated and broadened in scope by increasing the venous pressure moderately. Under such circumstances, transudation leading to edema takes place most abundantly from the venules. The permeability of the portion of the capillary web that is near the arterioles increases only when the venous pressure rises so high as to approximate that in the arteries. Under such circumstances, the gradient of permeability along the small vessels disappears, the capillaries and venules everywhere leaking fluid. The character of the vital staining under such circumstances indicates, like the evidence of previous work, that the gradient results from structural differentiation.

The mounting gradient of permeability along the small vessels of the corium is essentially unaltered by active hyperemia produced by heat, cold or light. Only when the vascular walls are so damaged that rapid leakage ensues, as shown by edema, does the permeability of the capillary web as a whole approximate that of the venules. It is plain that the normal gradient of vascular permeability depends on the integrity of the wall of the blood vessel. The method of experiment described can be utilized for a study of the functional changes that result in lesions due to burning and freezing.

AUTHORS' SUMMARY.

THE AGE FACTOR IN THE VELOCITY OF THE GROWTH OF FIBROBLASTS IN THE HEALING WOUND. E. L. HOWES and S. C. HARVEY, J. Exper. Med. **55**:577, 1932.

The velocity curve of fibroplasia in the healing of wounds in young rats reached its end-point three days ahead of a similar curve for adults. Strength and fibroplasia were manifest one day sooner than in the adults. A study of the increments of the curve showed that the rate of fibroplasia during the accelerated phase was less in the young, and that it lasted longer. Correspondingly, retardation appeared later and was less than in the curve for the adult rats. The retardation was even less than in the curve for adult rats on a high protein diet, in spite of the fact that in the latter curve there was a definite increase in the rate of fibroplasia. Healing in the young, therefore, is more rapid than in adults because fibroplasia begins earlier and is less retarded, not because the rate of fibroplasia is greater. Growth of the young is not hindered by the process of wound healing.

AUTHORS' SUMMARY.

RENAL THRESHOLDS FOR HEMOGLOBIN IN DOGS. J. A. LICHTY, JR., W. H. HAVILL and G. H. WHIPPLE, J. Exper. Med. **55**:603, 1932.

We use the term "renal threshold for hemoglobin" to indicate the smallest amount of hemoglobin that given intravenously will effect the appearance of recognizable hemoglobin in the urine. . . . Rest periods without injections cause a return of the renal threshold for hemoglobin toward the initial level — a recovery level. Injections of hemoglobin below the initial, but above the minimal, or depression, threshold level will eventually reduce the renal threshold for hemoglobin to its depression level. We believe that the depression, or minimal, renal threshold level due to repeated injections of hemoglobin is a little above

the glomerular threshold, which we assume is the base line threshold for hemoglobin. Our reasons for this belief in the glomerular threshold are given in this paper and in the other papers of this series.

AUTHORS' SUMMARY.

FAT MOBILIZATION IN STARVATION. J. H. DIBLE, J. Path. & Bact. **35**:451, 1932.

The degree of fat infiltration in the liver in starved rats is dependent on the quantity of fat available for mobilization in the animals' storage depots. Once the metabolism of starvation is established, this factor is the determining one and is independent of time. The histologic changes, acidosis and changes in the nonsaponifiable extractable material are discussed in their relationship to these findings.

AUTHOR'S SUMMARY.

EXPERIMENTAL ATHEROSCLEROSIS OF THE CORONARY ARTERIES OF RABBITS. K. WOLKOFF, Beitr. z. path. Anat. u. z. allg. Path. **85**:386, 1930.

On feeding of cholesterol to rabbits, Wolkoff demonstrated, after from 139 to 176 days, progressive focal subendothelial deposition of lipoids, which predominated about the origins of the coronary vessels and at their points of division. After the longer periods there were associated proliferation of the fixed cells, increase of elastic and collagenic tissue and presence of "xanthoma" cells. The media contained a little interstitial lipoid.

In rabbits studied from 100 to 1,003 days after cessation of the cholesterol feeding, there was noted gradual disappearance of the lipoid deposits with formation of intimal plaques composed of hyalinized collagenic fibers in which were embedded lipoid droplets, cholesterol crystals and calcium granules. The media underneath the plaques was frequently secondarily atrophied to almost complete disappearance.

Wolkoff considers this experimental coronary atherosclerosis, as regards both histologic aspects and distribution, very similar to the human disease, and therefore assumes the pathogenesis of both to be identical.

W. S. BOIKAN.

RELATIONSHIP BETWEEN CARBOHYDRATE METABOLISM AND MITOCHONDRIA IN THE LIVER. K. TANIGUCHI and M. HIKIMA, Beitr. z. path. Anat. u. z. allg. Path. **85**:565, 1930.

The normal lactic acid content of the blood was determined as from 20 to 28 mg. per cent. A rise to 30 mg. per cent in human subjects was correlated by biopsy with definite morphologic alterations in the mitochondria and in their distribution in the liver. The determination of lactic acid in the blood is therefore considered a sensitive and exact test for hepatic function.

W. S. BOIKAN.

RETINAL RESPIRATION AND AMINO-ACIDS. BRUNO KISCH, Biochem. Ztschr. **244**:459, 1932.

In contrast with tumor tissue, retina shows a definite respiratory increase on addition of glycocoll, alanine and phenylalanine. This effect is more marked in old than in fresh retinal tissue. In distinction from renal tissue, retinal responds less markedly to alanine and phenylalanine with respiratory increase than to serine, valine and sarcosine.

WILHELM C. HUEPER.

EXPERIMENTAL PRODUCTION OF FIBROUS OSTEITIS. E. RUTISHAUSER, Centralbl. f. allg. Path. u. path. Anat. **53**:305, 1932.

Human parathyroid glands were roughly sterilized in chloroform, macerated in salt solution and injected into guinea-pigs subcutaneously. In the majority of the animals abscesses developed, but Rutishauser feels that he has enough data

to summarize as follows: Fibrous osteitis can be produced in guinea-pigs by the injection of macerated human parathyroid tissue. The animals have an elevated calcium content of the blood. It is possible to see the first stages of the disease after thirty days; these are characterized by resorption processes and the formation of fibrous marrow. Suppuration does not cause the disease, because the picture can be duplicated by the subcutaneous injection of 3.5 Gm. of dextrose twice daily for about one hundred days. Schmidtman has produced it by the subcutaneous injection of ammonium chlorate and by the administration of viosterol.

GEORGE RUKSTINAT.

THE METABOLISM OF THE SUPRAVITAL NORMAL AND GOITROUS THYROID GLAND. B. WALTHARD, Ztschr. f. d. ges. exper. Med. **79**:451, 1931.

The metabolism of the normal thyroid gland of the wild rat and of different types of human goiter was studied by the method of Warburg. A simultaneous histologic examination of every specimen appeared to be valuable, because degenerative changes may influence the metabolism in the same way as does cell proliferation. The metabolism of the normal and the goitrous thyroid gland was found to be governed by the laws of Warburg. Normal thyroid tissue showed a high grade of oxidation and no aerobe fermentation of sugar. Diffuse goiters behaved like normal tissue as long as degenerative changes were absent. In parenchymatous adenomas (so-called fetal adenomas) a metabolic effect was observed typical for benign tumors, namely, high rate of oxidation and aerobe fermentation of sugar. Degenerative changes, as recognized histologically, were accompanied by decrease in respiration and increased aerobe glycolysis. The malignant goiters reacted like other cancerous growths, showing marked fermentation and diminished oxidation.

C. A. HELLWIG.

## Pathologic Anatomy

CONTRACTED KIDNEYS IN CHILDHOOD. M. KLEIN, Frankfurt. Ztschr. f. Path. **41**:317, 1931.

The author describes one case of malignant nephrosclerosis and two cases of chronic glomerulonephritis (secondary contracted kidneys) occurring in children. A short review of reported cases of malignant nephrosclerosis is also given. The differences between the two types of kidneys are discussed. In cases of malignant nephrosclerosis, endarteritis and periarteritic changes combined with necrosis of the walls of the arterioles are found. These changes extend into the vasa afferentia and capillaries of the glomeruli. In cases of chronic glomerulonephritis, blood vessel changes may be present, but endarteritis and arterionecrosis are not characteristic. In cases of malignant nephrosclerosis, inflammatory changes within the glomeruli may be the result of primary inflammatory changes of the blood vessels. The inflammatory changes of the glomeruli are not so severe and diffuse as in cases of chronic glomerulonephritis. The arteriolosclerosis leads to disappearance of glomeruli, without accompanying inflammatory changes of the glomerulus. Malignant nephrosclerosis does not occur secondary to "nephrocirrhosis arteriolosclerotica." The author believes that there are only nine proved cases of malignant nephrosclerosis in children on record, while twenty-four cases that have been reported to be such are doubtful. Chronic inflammatory contracted kidneys (chronic glomerulonephritis) in children was found described in the literature twenty-two times. The blood vessel changes that are found in the spleen, liver, pancreas, brain, thymus and suprarenal glands are not inflammatory. Morphologically, they resemble the changes seen in arteriosclerosis. They probably are the result of the increased pressure occurring in renal insufficiency.

O. SAPHIR.

THE PATHOGENESIS OF A RARE MALFORMATION OF THE HEART (COR TRIATRIATUM). J. HAGENAUER, Frankfurt. Ztschr. f. Path. **41**:332, 1931.

Cor triatriatum in a 4 months old child is reported. The heart was enlarged owing to marked hypertrophy of the right ventricle; the left ventricle was small and gave the impression of being an appendage to the right ventricle. The right auricle was dilated and revealed the normal openings of the superior and inferior vena cavae. The interauricular septum showed an opening that led from the right into a small left auricle. This left auricle had no communication with the left ventricle, but formed a small blind-ending sac. The four pulmonary veins, however, opened into this auricle. When the left ventricle was opened, it was noted that it led through a normal mitral valve into a second left auricle. This second auricle revealed no communications with the first left auricle or with the pulmonary veins. A small auricular appendage, however, was attached to it. An open foramen ovale led from the second left auricle into the right auricle. The blood stream apparently flowed from the pulmonary veins into the first left auricle and from there through the open intra-auricular septum into the right auricle. Some of the blood passed into the right ventricle and some through the open foramen ovale into the second left auricle and from there into the left ventricle and the aorta. The possible conditions leading to this rare malformation are discussed. The underlying cause is apparently a secondary occlusion of the pulmonary vein, which primarily was open.

O. SAPHIR.

THE MECHANISM OF THE FORMATION OF CARDIAC THROMBI. M. PLONSKIER, Frankfurt. Ztschr. f. Path. **41**:357, 1931.

In a 6 year old girl, autopsy revealed endocarditis of the tricuspid and pulmonary valves. In addition, an open interventricular septum was found. The endocardium of the right ventricle in an area just opposite the septal defect revealed a thrombus. The author believes that the force of the blood stream coming from the open interventricular septum and directed on the right ventricular endocardium, combined with the force of the normal systolic blood stream, led to the production of endocardial thickenings in a circumscribed area. The thickened endocardium became a fitting location for the thrombus. Because of the fact that bacteria were found only on the surface of the thrombus, and not in the midportion or base, the author does not believe that a localization of bacteria was responsible for the formation of the thrombus. He is of the opinion that cardiac weakness in the course of a severe infectious disease causing slow circulation led to the formation of the thrombus in an area that was predisposed to such formation by endocardial changes.

O. SAPHIR.

CIRCUMSCRIBED OSTEOPOROSIS OF THE CRANIUM. W. SCHELLENBERG, Frankfurt. Ztschr. f. Path. **41**:423, 1931.

In a 40 year old man, the clinical diagnosis was: frontal sinusitis, with erosion and perforation of the frontal bone, and collection of air extradurally. An operation was performed to remove the air. The patient died shortly afterward. At autopsy, a cyst the size of a goose egg was present in the brain substance between the right parietal and occipital lobes. The cyst, which was filled with a clear liquid, did not communicate with the ventricular system. The left portion of the skull was much softer than the right. In the former, differentiation between the external and internal tables and the diploe was very indistinct. Histologic examination of these portions revealed circumscribed osteitis fibrosa. The relation between this disease and Paget's disease is discussed. The cyst in the brain is regarded as a "tied-off (*abgeschnürte*) ventricular cyst."

O. SAPHIR.

THREE CASES OF SPECKLED SPLEEN (MULTIPLE NECROSIS OF THE SPLEEN), WITH SPECIAL REFERENCE TO CHANGES IN THE KIDNEYS. E. ADOLPHS, Frankfurt. Ztschr. f. Path. **41**:435, 1931.

In three cases of speckled spleen, many areas of necrosis were found in the splenic tissue, caused by diffuse arteriolonecrosis. While in two cases all of the larger arteries of the spleen also showed simple arteriosclerosis, in the last case only arterionecrosis was revealed. In all three cases, severe lesions of the kidneys were found. In the first two instances, there was also chronic glomerulonephritis, with arteriolonecrotic changes corresponding to those seen in malignant sclerosis or malignant arteriolonecrosis of the kidney. These findings are compared with those in simple arteriolosclerosis of the kidney. Even though in both conditions (arteriolonecrosis and arteriolosclerosis) hyalinization and lipoid degeneration are present in the arterioles, the appearance of a fibrinous exudate extending to the adventitia and to the surrounding tissues, necrosis and the presence of polymorphonuclear leukocytes are characteristic of arteriolonecrosis. The lumina of the arterioles in arteriolosclerosis are small or obliterated. In arteriolonecrosis, however, they may be wider than normal, probably because of the pressure exerted by the blood on the necrotic walls of the vessels. The question of whether arteriolonecrosis is the sequel of arteriolosclerosis is discussed. Because of the finding of arteriolonecrosis in the kidney in the third case without arteriolosclerosis, a relationship between these conditions seems questionable. The second case also showed a very recent arteriolonecrosis of all organs, especially of the skin, tongue, myocardium intestines and spleen. Some similarity of these diffuse lesions and those found in periarteritis nodosa is also discussed. The author believes that arteriolonecrosis occurs especially in kidneys showing chronic inflammatory lesions. The changes in the spleen are similar to those found in the kidneys. They are the result of arteriolonecrosis. In regard to the etiology of the lesions of the blood vessel, the author is inclined to believe in the hypothesis of Ricker, who stated that the necrosis of the wall of the blood vessel is the result of a marked irritation of the vasomotor nervous mechanism, with resulting paralysis of the walls. The necrosis is caused by the stoppage of the circulation of the tissue fluids in the walls.

O. SAPHIR.

ADIPOSOGENITAL DYSTROPHY. H. HEINRICHS, Frankfurt. Ztschr. f. Path. **41**:512, 1931.

In a 70 year old man, there was marked fibrosis of the capsule of the anterior lobe of the hypophysis. The fibrosis extended into this lobe and had led to a partial destruction of the tissue. The patient showed not only pituitary nanosoma but also the characteristic picture of adiposogenital dystrophy, with retardation of growth and hypoplasia of the testes.

O. SAPHIR.

ANATOMIC CHANGES OF HEART AND BLOOD VESSELS IN SEPTIC SCARLATINA. H. SIEGMUND, Verhandl. d. deutsch. path. Gesellsch. **26**:231, 1931.

In fifty-six autopsies on children who had died during an epidemic of scarlet fever, typical nodular infiltrations were found in the endocardium and in the walls of veins of internal organs, namely, spleen, liver, kidneys and suprarenal glands, in 90 per cent. In the aorta, perivascular infiltration of the vasa vasorum was often present. In those who died about eight weeks after the onset of the disease, nodules were found in the heart muscle and in the endocardium which had the same structure as the rheumatic bodies of Aschoff. The same changes were noticed in the peritonsillar tissue. The author regards these lesions as allergic reactions of a sensitized organism against streptococcic infection. In all his cases, hemolytic streptococci were cultivated from the blood at autopsy.

C. ALEXANDER HELLWIG.

RETICULO-ENDOTHELIAL SYSTEM AND AMYLOID. H. J. ARNDT, Verhandl. d. deutsch. path. Gesellsch. **26**:243, 1931.

In 100 horses used in the production of antitoxin at the Behring works at Marburg, Arndt and Doerken studied the morphologic aspect of immunobiologic processes, especially the behavior of the reticulo-endothelial system and the formation of amyloid. In the livers of the horses characteristic changes were observed: diffuse swelling of the endothelial cells, nodular granulomas and endophlebitic proliferation. These changes suggest that the antibodies are formed in the reticulo-endothelial system. In 60 of the 100 horses amyloid was demonstrated, most frequently in the spleen, less often in the liver and only rarely in other organs. Chemical analysis of the amyloid gave results similar to those obtained by analysis of human amyloid. There seems to be a relationship between the formation of the amyloid and the reaction of the reticulo-endothelial cells. The latter is regarded as the initial stage of amyloidosis. On the other hand, resorption of amyloid by reticulo-endothelial cells is suggested by the histologic observations.

C. ALEXANDER HELLWIG.

## Pathologic Chemistry and Physics

PULMONARY GAS ABSORPTION IN BRONCHIAL OBSTRUCTION. P. N. CORYLLOS and GEORGE L. BIRNBAUM, Am. J. M. Sc. **183**:317, 1932.

Experimental methods have been devised which give evidence that when a bronchus is completely obstructed the entrapped alveolar air rapidly undergoes qualitative and quantitative changes as determined by successive gas analyses. Qualitatively, the percentages and partial pressures of the gases comprising the alveolar air tend to, but never reach, an equilibrium with the gases of the venous blood. Quantitatively, the entrapped alveolar gases pass through the respiratory membrane into the blood circulating in the peri-alveolar capillaries until complete airlessness of the involved area is produced. The mechanism of production of atelectasis in the compressed lung (pneumothorax, pleural exudate, intrathoracic tumors, etc.) is exactly the same as in bronchial obstruction. Besides the gases of the air, diffusion of other gases was studied by introducing them into a lung previously rendered atelectatic. The different gases used in these experiments were: (*a*) active gases, oxygen and carbon dioxide; (*b*) neutral gases, hydrogen, nitrogen and helium; (*c*) anesthetic gases or vapors, ether, ethyl chloride, nitrous oxide and ethylene. The new experimental methods allow direct vision of the pulmonary changes occurring during the experiment. Nitrogen in the respiratory air plays the part of a "mechanical buffer," retarding the absorption of more diffusible and more soluble gases. This experimental work has allowed the formation of a theory on the mechanism of atelectasis based on the physiology of exchange of gases in the lung.

AUTHORS' SUMMARY.

WATER AND OTHER INORGANIC CONSTITUENTS IN THE HEART MUSCLE OF TUBERCULOUS PATIENTS. L. C. SCOTT, Am. Rev. Tuberc. **23**:429, 1931.

The principal inorganic constituents of fourteen hearts from tuberculous patients agree fairly well with those of an equal number of hearts from persons dying from various other diseases with the sole exception of the water content. The latter is sufficiently in excess of the average found in other diseases to warrant the assumption that the excess is characteristic of this disease, especially when the disease has been of comparatively long standing.

H. J. CORPER.

A METHOD FOR THE DETERMINATION OF THYROXINE IN THE THYROID. J. P. LELAND and G. L. FOSTER, J. Biol. Chem. **95**:165, 1932.

An improved method is described for the isolation and estimation of the thyroxine content of human thyroid tissue. Approximately 25 per cent of the total iodine of fifty-two glands was present as thyroxine.

E. R. MAIN.

NORMAL PLASMA PROTEIN CONCENTRATION IN SPITE OF LOSS BY BLEEDING. C. W. BARNETT, R. B. JONES and R. B. COHN, J. Exper. Med. **55**:683, 1932.

From 25 to 100 cc. of blood plasma was removed daily from five dogs, the red cells being returned to the circulation in Locke's solution. In no case was there a significant drop in the protein concentration of the plasma. A gravimetric method for the determination of the total amount of protein in the plasma is described. A case of cirrhosis of the liver is reported in which over 10 Gm. of protein was lost daily in the ascitic fluid during a period of seven months without any lowering of the protein concentration of the plasma. The constancy of the protein level and the adequacy of the mechanism of regeneration are pointed out.

AUTHORS' SUMMARY.

THE BIOLOGIC ACTION OF ULTRAHIGH FREQUENCY CURRENTS. R. A. HICKS and W. T. SZYMANOWSKI, J. Infect. Dis. **50**:466, 1932.

For the moment, no studies in this field can be regarded as final, especially with respect to the interpretation of the results. If one considers the gamut of wavelengths, each one of which may offer a distinctive action, if one considers the enormously variable factors in thermal conditions, character of medium, period of exposure, potential across the plates and different conditions of tuning, the problem, from the point of view of its physical set up, becomes very extensive. If, in addition, one considers the number of bacterial variants, as well as other biologic substances that might be studied under the whole scale of physical conditions possible, it becomes obvious that no final statement may be made with regard to the biologic action of ultrahigh frequency currents. It is possible, however, to say from the work now reported that at least there is no biologic action on the substances mentioned under the described conditions of exposure to ultrahigh frequency fields. It is also probable that indefinite extension of this study may not lead to a vigorous and readily detectable direct biologic action without some marked technical advance beyond that of the present day. It must be borne in mind, however, that almost infinite possibilities exist for the development of this field, and accordingly negative conclusions at this time are restricted to the experimental conditions employed.

AUTHORS' SUMMARY.

ERGOTHIONEINE CONTENT OF THE BLOOD IN HEALTH AND DISEASE. H. B. SALT, Biochem. J. **25**:1712, 1931.

An improved method is described for the estimation of ergothioneine in blood. Ergothioneine is not present in the blood plasma of normal persons. From 3 to 12 mg. per hundred cubic centimeters is found in the erythrocytic fraction of blood obtained from normal persons and from persons with diseases other than diabetes. Slightly higher values are observed in diabetes.

E. R. MAIN.

BLOOD PHOSPHATASES. JEAN ROCHE, Biochem. J. **25**:1724, 1931.

The phosphatase in the erythrocytes appears to differ from that in the serum and leukocytes. The latter may be identical with the phosphatase of the kidneys and intestines. Phosphatases hydrolyze mono-substituted glycerophosphates, but have no appreciable action on di-substituted esters. They synthesize phosphoric esters from inorganic phosphate and the various alcohols.

E. R. MAIN.

FERMENTABLE SUGAR IN NORMAL URINE. V. J. HARDING and D. L. SELBY, Biochem. J. **25**:1815, 1931.

Sugar capable of being fermented by yeast is not present in the urine of normal persons following a twelve hour fast. Small amounts may be present immediately

following the ingestion of fructose or large quantities of fruit. Although glycosuria does not occur following the ingestion of 50 Gm. of dextrose in the early morning after a twelve hour fast (the dextrose tolerance test), it may occur following the ingestion of sugar at 4 p. m.

E. R. MAIN.

SPERMINE IN HUMAN TISSUES. G. A. HARRISON, Biochem. J. **25**:1885, 1931.

The human prostate gland contains more than 300 mg. of spermine phosphate per hundred grams of tissue. The concentration of the base per hundred grams of seminal plasma is approximately 100 mg. From 1 to 9 mg. per cent is present in the testis, approximately 16 is in the pancreas, from 3 to 8 in the spleen, from 5 to 6 in the kidney, from 2 to 11 in the liver, from 3 to 5 in the lung, from 2 to 3 in the brain and from 1.5 to 2 in the heart. A trace of spermine was observed in the dried feces; none was found in the bone-marrow, blood or sputum. The derivation of spermine from the prostate gland, rather than from the testicle, is confirmed by the absence of the substance in the semen of the skull. The bull does not have a truly functional prostate gland.

ARTHUR LOCKE.

AN IN VITRO EFFECT OF ANTI-NEURITIC VITAMIN CONCENTRATES. N. GAVRILESCU and R. A. PETERS, Biochem. J. **25**:2150, 1931.

The amount of oxygen absorbed by finely minced preparations of the lower parts of the brains of normal pigeons is increased approximately 40 per cent when the measurements are made in an atmosphere of oxygen in place of air. The amount of oxygen absorbed by similar preparations of brain from avitaminous ($B_1$) pigeons is not only less than normal, but is markedly less influenced by the oxygen content of the atmosphere in which the measurements are made. This curious difference is less manifest when the preparations are admixed, in vitro, with a concentrate containing vitamin $B_1$. The restorative action of the vitamin appears to be catalytic and not due to substances other than the vitamin adventitiously present in the concentrate. Vitamin $B_1$ appears to be directly concerned in the regulation of the respiration and function of the lower parts of the pigeon brain.

ARTHUR LOCKE.

A PIGMENT IN THE SWEAT AND URINE OF CERTAIN SHEEP. C. RIMINGTON and A. M. STEWART, Proc. Roy Soc., London, s. B. **110**:75, 1932.

The golden-brown coloration of the wool fiber of many sheep appears to be due to a pigment, lanaurin, which is secreted in the sweat. The pigment may be isolated from both the wool and the urine. It is a pyrrolic complex and probably occupies an intermediate position between the bile pigments and fully condensed melanin. The condition in sheep resembles familial acholuric jaundice in man. Both phenomena may be due to a hereditary tendency to hyperactivity on the part of the cells of the reticulo-endothelial system, with increased destruction of hemoglobin. Lanaurin may be considered to be derived from hemoglobin and to be excreted by the renal and sudorific systems.

E. R. MAIN.

COLORIMETRIC $p_H$ OF MALIGNANT CELLS IN TISSUE CULTURE. R. CHAMBERS and R. J. LUDFORD, Proc. Roy. Soc., London, s. B. **110**:120, 1932.

The intracellular hydrogen ion concentration of mouse tumors in culture is $p_H$ 6.8 $\pm$ 0.1, a value comparable to that observed in normal cells of a similar nature. After injury or cytolysis, the $p_H$ value of both tumor and normal cells decreases to 5.6 or less. The intranuclear hydrogen ion concentration is $p_H$ 7.2 and does not appear to be lowered following injury.

E. R. MAIN.

RETENTION OF MERCURY IN THE BODY. HOLTZMANN, Arch. f. Hyg. **106**:377, 1931.

Mercury was found at autopsy in the lungs of guinea-pigs poisoned by the continued respiration of air containing droplets of this metal. Appreciable amounts were found in the kidneys, through which it is slowly eliminated. Much smaller amounts were found in the liver.

ARTHUR LOCKE.

SIGNIFICANCE OF COPPER, ZINC AND MANGANESE IN PATHOLOGY. W. HERKEL, Beitr. z. path. Anat. u. z. allg. Path. **85**:513, 1930.

By prolonged feeding of various copper salts to rabbits and rats, Herkel could produce increased storage of copper in the liver, but not cirrhosis. He found increased copper in the liver not only in patients with hematochromatosis but also in those with nonpigmentary cirrhosis, in pregnant women and in nursing infants. The need of rapidly growing tissues for copper is suggested as the possible explanation. Zinc values showed no significant variations.

W. S. BOIKAN.

OCCURRENCE OF GLYCOGEN IN ADIPOSE TISSUE. F. RICHTER, Beitr. z. path. Anat. u. z. allg. Path. **86**:65, 1931.

Glycogen can be demonstrated in the fat tissue of the white rat if, after preliminary starvation, carbohydrates are fed. It represents an intermediate stage in the synthesis of fat. But the reverse—the appearance of glycogen during the utilization of fat—does not occur. Epinephrine and insulin do not lead to storage of glycogen in the fat tissue. The glycogen content of fetal tissue is independent of the maternal. The fat tissue of fetal rats as well as that of the human cadaver contains no glycogen.

W. S. BOIKAN.

POTASSIUM CONTENT OF BONE MARROW IN CANCER. T. HOFFMANN, Biochem. Ztschr. **243**:145, 1931.

The quantitative analysis of bone marrow during the age of growth showed a high content of potassium, dropping to from one fourth to one fifth of this value after the end of this period. In the presence of carcinoma, a new accumulation of potassium in the bone marrow is seen. The values obtained are at least twice as large as those for the normal, noncarcinomatous adult. The sodium content of the bone marrow shows similar, but less constant, variations. The variations in the calcium content have no relations to the growth.

WILHELM C. HUEPER.

PHENOL DERIVATIVES IN URINE. OTTO FUERTH and RUDOLF SCHOLL, Biochem. Ztschr. **243**:276, 1931.

Three types of phenol derivatives may occur in the urine: (1) substances that can be removed by steam distillation, such as phenol and cresol; (2) substances that can be extracted with ether, such as *p*-oxyphenyl propionic acid, *p*-oxyphenyl acetic acid, *p*-benzoic acid, *p*-oxyphenyl lactic acid and *p*-oxyphenyl pyruvic acid (which are derivatives of tyrosine through deamidization); (3) substances which are neither ether-soluble nor removable by steam distillation, and which are designated as oxyproteinic acids, contributing to the diazo reaction. Also chromogen belongs in this group.

Causes for their appearance in the urine are: (1) increased putrefaction of protein in the intestine, (2) disturbed function of the liver (acute yellow atrophy, phosphorus poisoning, etc.) and (3) increased decomposition of protoplasm in the living organism.

The phenol fraction that can be distilled off is clinically unimportant. The ether-soluble fraction can be determined colorimetrically, if a larger amount of urine (1,000 cc.) is acidified with sulphuric acid till congo red paper turns blue,

and then concentrated in a vacuum (35 mm. of pressure) and nitrogen current at low temperature to 100 cc., and finally shaken twice with 25 cc. of ether. The ether is washed twice with water and then shaken with a small amount of 10 per cent sodium hydroxide, which extracts the phenol substances. The aqueous layer is acidified with 50 per cent sulphuric acid, and after brief boiling, decolorized with charcoal and examined with Millon's reagent colorimetrically. A 1 per cent tyrosine solution in 5 per cent sulphuric acid is used as a standard. The normal human urine contains between 0.0043 to 0.0050 mg. of phenol per hundred cubic centimeters, calculated as tyrosine. The ether-insoluble fraction can be determined in the urea-free fraction of the urine, which is obtained after the Mörner-Sjöquist method by precipitation with a solution of barium hydrate (15 Gm. in an alcohol-ether mixture—ratio 2:1). The barium hydrate is removed by sulphuric acid; interfering substances, by tungstic acid; these again are removed by the addition of quinine in excess, which in its turn is removed by the addition of sodium hydroxide. The phenol can then be determined with Millon's reagent. Normal urine contains only traces of these substances, which cannot be determined colorimetrically. The determination of indican in the urine by the method of Wang was found to be unreliable. The normal indican content of human urine estimated with the colorimetric method, with sodium indigo-sulphonic acid used as a standard, varies between 0.8 and 1.3 mg. per hundred cubic centimeters. The amount of ether-soluble phenol remains within normal limits in pathologic urine, while the amount of the ether-insoluble fraction increases considerably in certain conditions, reaching values up to from 36 to 104 mg. per hundred cubic centimeters (acute yellow atrophy). Similar values were obtained in cases with functional disturbances of the liver (in catarrhal jaundice, but not in cirrhosis), in severe intestinal disturbances, and in advanced tuberculosis with positive urochromogen reaction. In schizophrenic patients, only exceptionally increases of the ether-insoluble fraction were seen. There is no relation between the urinary indican due to putrefaction of protein and the ether-insoluble fraction of phenols.

WILHELM C. HUEPER.

TITRIMETRIC DETERMINATION OF AMINO-ACIDS IN BLOOD SERUM. KONRAD L. ZIRM and JOHANN BENEDICT, Biochem. Ztschr. **243**:312, 1931.

Three cubic centimeters of serum is deproteinized with colloidal iron hydroxide under heating. The hot fluid is centrifugated, and the clear supernatant fluid is evaporated over a water bath. The dried material is dissolved in water, and after addition of L-naphthyl red it is titrated against a water control with a fortieth-normal alcoholic hydrochloric acid solution. By this method, the strongly basically reacting nitrogen-containing groups are determined. If instead of naphthyl red, 2, 4, 2′, 4′, 2″ pentamethoxytriphenylcarbinol is used, a preliminary titration of the control can be omitted. Normal serums have an amino-nitrogen level of from 5.4 to 8 mg. per hundred cubic centimeters. The Van Slyke method gives slightly higher values, owing to partial inclusion of urea nitrogen in the values obtained. The results agree well with those obtained by the Folin method.

WILHELM C. HUEPER.

## Microbiology and Parasitology

THE EFFECT OF TESTICULAR PASSAGE ON THE VIRUS OF HERPES. W. SMITH, J. Path. & Bact. **34**:747, 1931.

The power of causing specific adrenal lesions and cutaneous reactions in rabbits is probably common to all strains of herpes virus, the production of such lesions being dependent on the quantity of virus inoculated. The testis of the rabbit provides a better culture medium for the growth of herpes virus than the brain; this holds true even for intensely neurotropic strains. The nonspecific factor

described by Duran-Reynals as enhancing the virulence of vaccinia virus does not account for the greater infectivity of herpes testis as compared with herpetic brain.

AUTHOR'S SUMMARY.

EXPERIMENTAL POLIOMYELITIS FROM INTRATHECAL INOCULATION OF THE VIRUS. E. W. WESTON, J. Path. & Bact. **35**:41, 1932.

After intrathecal inoculation of poliomyelitic virus, the distribution of both the virus and the lesions in the cerebral hemispheres is strikingly different from that of the maximum meningitis or of the deepest staining with dyestuffs injected into the fluid. Frequently the earliest lesions are situated in the floor of the fourth ventricle, into which under the conditions of the experiment the virus regurgitates at operation, and the influence of axonic transmission in their subsequent spread is again evident. It is suggested that penetration of the nerve tissues may occur through the ependyma of the fourth ventricle, but an attempt to demonstrate the permeabiliy of a purely meningeal surface was unsuccessful. Considering the pathogenesis of human poliomyelitis, it is concluded that no evidence available speaks against an axonic entry of the virus or necessitates the participation of the cerebrospinal fluid in its spread through the nervous system.

AUTHOR'S SUMMARY.

THE BLOOD SUGAR AND PHOSPHORUS IN RABBITS AFTER THE INJECTION OF SUSPENSIONS OF DEAD BACTERIA. M. E. DELAFIELD, J. Path. & Bact. **35**:53, 1932.

Intravenous injections of suspensions of dead gram-positive organisms into rabbits produced no obvious illness. Ten different organisms were used. With the exception of Streptococcus pneumoniae, which caused a fall in the organic phosphorus of the blood, none of the organisms evoked any significant change in the sugar or the phosphorus level. Eight of the twelve gram-negative organisms tested produced obvious illness of the animals, with hyperglycemia and low inorganic phosphorus at two hours after injection, followed at twenty-four hours by a lower level of sugar and a higher level of phosphorus. Two of the twelve gram-negative organisms produced the chemical response without illness. Two of the twelve gram-negative organisms produced no illness and no typical chemical response. Staphylococcus aureus and Strep. viridans, rendered in part gram-negative by long growth in broth, were inert as were also the bacterial filtrates of these organisms. There appears to be a significant correlation between the changes in the sugar and the phosphorus content of the blood in the first twenty-four hours after injection. High inorganic phosphorus is always found when the animal is gravely ill at any time subsequent to the first twenty-four hours after injection.

AUTHOR'S SUMMARY.

RELATIVE INCIDENCE OF HUMAN AND BOVINE TUBERCLE BACILLI IN TUBERCULOUS MENINGITIS IN ENGLAND. A. S. GRIFFITH, J. Path. & Bact. **35**:97, 1932.

Cultures of tubercle bacilli have been obtained from the cerebrospinal fluid in thirty new cases of tuberculous meningitis (years 1930 and 1931), twenty-nine of which occurred in children under 10 years and one in an adult. Of the twenty-nine children, twenty were infected with bacilli of bovine type. The adult was also infected with bovine bacilli. Twenty-seven of the cases occurred in Leeds, and in eight (29.6 per cent) of these cultures yielded bovine tubercle bacilli. Of the remaining cases due to infection with bovine bacilli one was derived from Lancashire and one from Lincolnshire. The total number of cases of tuberculous meningitis in which cultures have been obtained from cerebrospinal fluid drawn during life is sixty-three. Of these nineteen (30.2 per cent) were due to bovine bacilli. With this percentage as a basis it is estimated that in England and

Wales upward of seven hundred persons died of tuberculosis of the central nervous system caused by bovine tubercle bacilli in each of the three years 1928, 1929 and 1930.

AUTHOR'S SUMMARY.

SCARLATINAL STREPTOCOCCI IN NONSCARLATINAL INFECTIONS. V. D. ALLISON, Lancet **2**:844, 1931.

Of 396 strains of hemolytic streptococci isolated from nonscarlatinal infections, only 8 (2 per cent) were found to belong to one or other of the four main serologic types of scarlatinal streptococci. The results indicate the high degree of specificity of the scarlatinal streptococci, as 63 per cent of hemolytic streptococci from scarlatinal patients can be typed serologically. Among the 8 typed strains, a type I strain and a type III strain were isolated from uterine cervical swabs in cases of puerperal infection, while a type I strain and a type III strain were isolated from throat swabs of midwives in attendance on the respective patients. These results corroborate those recently shown by Smith and support the view of many clinicians that puerperal infection may arise by infection from the air passages of persons in attendance on the patients. In 100 consecutive cases of diphtheria and 100 consecutive cases of measles, 62 strains and 32 strains, respectively, of hemolytic streptococci were isolated, but none were placed in any of the main serologic types of scarlatinal streptococci.

AUTHOR'S SUMMARY.

THE ULTRAVIRUS OF TUBERCULOSIS. F. VAN DEINSE, Ann. Inst. Pasteur **47**:135, 1931.

The ultravirus, when inoculated into the living guinea-pig, develops rapidly in pus formed within the peritoneal cavity. Calcium phosphate seems to aid in the development if injected several days after the introduction of tuberculous filtrate. Acid-fast organisms may be demonstrated in animals killed from two to four days after inoculation. The observations are offered, incidentally, as a means of differentiating the ultravirus from the visible bacilli.

M. S. MARSHALL.

THE ETIOLOGY OF ULCERATIVE COLITIS. R. BUTTIAUX and A. SÉVIN, Ann. Inst. Pasteur **47**:173, 1931.

An extensive study of ulcerative colitis is concluded with the following résumé: ". . . We think that the infectious etiology of ulcerative colitis should be interpreted in the following manner. There exist forms of chronic colitis that arise from specific organisms of this disease. These organisms are rare; only two of them have been recognized, Bargen's organism (a diplococcus) and ours (also a diplococcus).

"Other forms of ulcerative colitis which we designate as 'recalled' (de rappel) are due to the awakening of organisms that have previously provoked a general infection, cured at the moment when intestinal damage occurs.

"A third category of colitis which we designate as 'de sortie' by analogy to that which occurs in grip, for example, is due to exaltation of virulence on the part of organisms common in the intestines and to their localization at certain points where the resistance has momentarily been diminished owing to exaggerated parasitism or to any other cause (multiple digestive insufficiencies, general diminution of the resistance of the patient by an intercurrent infection, etc.)."

M. S. MARSHALL.

SILENT TYPHUS FEVER IN MAN. J. TROISIER, R. CATTAN and MLLE. SIFFERLEN, Ann. Inst. Pasteur **47**:492, 1931.

The question of the specific etiology of the exanthematic fever occurring around the Mediterranean basin was approached experimentally. Dog ticks, Rhipicephalus

sanguineus, the demonstrated vectors, were collected, ground and injected into a man, in whom an infection inapparente, as described by Nicolle, was induced. The Weil-Felix reaction was positive, but no systemic or local disturbance appeared. Transfer to a second subject resulted in similar observations. The blood of the first patient, injected into a monkey, induced a typical fever, a discrete exanthem and a Weil-Felix reaction. The blood of the monkey induced fever in guinea-pigs. The virus of the blood of the first human subject was also apparently passed through a guinea-pig to a monkey to a human subject, and through a series of three guinea-pigs to a monkey. Histologic study confirmed these observations (thrombophlebitis and perivascular infiltration). This virus of man, monkeys and guinea-pigs transmitted by the dog tick appears to be closely allied with typhus fever.

M. S. MARSHALL.

LIPASE CONTENT OF THE SERUM OF TUBERCULOUS CHILDREN. A. GRADNAUER, Beitr. z. Klin. d. Tuberk. **77**:725, 1931.

The lipase content was determined by the stalagmometric method of Rona and Michaelis, modified by Willstätter and Memmen. The serum of healthy children and adults shows, on the average, about the same amount of lipase, although large individual variations occur; that of patients with prognostically unfavorable pulmonary tuberculosis shows the level of lipase to be very low. A correlation between the lipase content and the general condition, the extent of the pulmonary involvement and the anatomic character of the pulmonary lesion is not demonstrable. Very low lipase values in pulmonary tuberculosis indicate a hopeless prognosis, but the same is not true in other organic involvement.

MAX PINNER.

FILTRABLE FORMS OF THE TUBERCLE BACILLUS. D. SZÜLE, Beitr. z. Klin. d. Tuberk. **78**:18, 1931.

Filtrates of tuberculous organs and of pure cultures were inoculated in a variety of mediums. In no case was growth obtained. Inoculation of animals with the same filtrates yielded negative results.

MAX PINNER.

TUBERCULOSIS OF THE BRONCHIAL NODES AS A CAUSE OF SEVERE HEMOPTYSIS IN OLD PEOPLE. A. ARNSTEIN, Beitr. z. Klin. d. Tuberk. **78**:55, 1931.

Hemoptysis caused by perforation of a tuberculous or anthracotic lymph node simultaneously into the bronchial tree and into a blood vessel is not a rare occurrence in old people. Ten cases are reported in some detail.

MAX PINNER.

SERUM CHOLESTEROL IN HIGH ALTITUDES AND ITS RELATION TO TUBERCULOSIS. A. BEHRMANN, Beitr. z. Klin. d. Tuberk. **78**:214, 1931.

Studies on twelve normal persons and on forty-seven tuberculous patients failed to show a definite influence of high altitude on the serum cholesterol. With productive lesions, the cholesterol content is normal or increased. In patients with progressive involvement and particularly in those who are cachectic, subnormal values are frequently found.

MAX PINNER.

THE MAIN FORMS OF TUBERCULOSIS IN AUTOPSY MATERIAL. H. RÜDEL, Beitr. z. Klin. d. Tuberk. **78**:243, 1931.

This paper is based on the observations in the Pathologic Institute at Heidelberg from 1911 to 1930. During this time, a total of 14,967 autopsies were made. In 1,816 cases, making 12.1 per cent of the total, the main diagnosis was tuberculosis. Death from tuberculosis occurs with the highest frequency in the first

year of life, during puberty and in the third decennium. Generalizing forms of tuberculosis comprised 47 per cent of all cases of tuberculosis, and miliary forms constituted 42 per cent of all generalized forms. Of 856 cases of generalized tuberculosis, 73 were cases of acute miliary tuberculosis.

MAX PINNER.

TUBERCULOUS ENDAORTITIS. J. HAAS, Beitr. z. Klin. d. Tuberk. **78**:315, 1931.

In a man 58 years old who had died of subacute miliary tuberculosis a polypoid mass, the size of a bean, was found on the intima of the arcus of the aorta. This proved to be a slightly encapsulated caseous tuberculous mass containing large numbers of tubercle bacilli. Since caseous material easily oozed from this mass, it is assumed that it was the feeding focus for the miliary propagation. This focus, according to histologic studies, must have started in the intimal layer. No tuberculous foci were found in the adventitial layer.

MAX PINNER.

THE BIOLOGIC PROPERTIES OF SEVENTY-EIGHT STRAINS OF TUBERCLE BACILLI ISOLATED FROM INFANTS IN LÜBECK. H. J. TIEDEMANN and A. HÜBENER, Beitr. z. Klin. d. Tuberk. **78**:520, 1931.

The strains were obtained both from clinical material and from autopsy material from infants who had been vaccinated in Lübeck, supposedly with B C G. Only two of the strains were not pathogenic for guinea-pigs; these behaved in the same manner as does an undoubted B C G strain. One of these avirulent strains was obtained from autopsy material from a child who had died of a nontuberculous infection; the only tuberculous lesions found were small caseous foci in the mesenteric lymph nodes. The second avirulent strain was obtained from the gastric content of a child who completely recovered from an undiagnosed disease. All other strains were virulent for guinea-pigs, but not for rabbits. Their virulence for guinea-pigs was rather slight, but quite uniform, although they were derived from children with progressive, fatal and healing forms of the disease. Since even the strains from children who had died from acutely progressive tuberculosis showed low virulence for guinea-pigs, it must be concluded that virulence for guinea-pigs is in no way parallel to that for man. The strain "Kiel" which was present in the laboratory in Lübeck at the time of vaccination, and which is an atypical human strain, shows approximately the same degree of virulence for guinea-pigs as do the strains isolated from infants.

MAX PINNER.

THE PRODUCTION OF A GROWTH REGULATOR BY ASPERGILLUS NIGER. P. BOYSEN-JENSEN, Biochem. Ztschr. **239**:243, 1931.

Peptic digestion of fibrin, hemoglobin and casein does not result in production of a growth regulator. Aspergillus niger cultured in solutions of peptone or hemoglobin produces a growth regulator in considerable amounts. As the formation of this growth regulator occurs also in liquid mediums, it is easy to obtain large amounts of it. The unit of the growth regulator is that amount which dissolved in 100 cc. of water plus agar causes a difference of 1 cm. in the distance from the convex to the concave side of the avenacoleoptile.

WILHELM C. HUEPER.

HYPERERGIC SKIN INFLAMMATION IN THE HOG. K. NIEBERLE, Verhandl. d. deutsch. path. Gesellsch. **26**:239, 1931.

While the septic erysipelas of the hog is characterized by confluent erythema affecting the skin of the abdomen and thighs, the so-called chronic erysipelas shows diffuse necrosis of the skin on the back and breast. In the necrotic areas, Bacillus rhusiopathiae suis can be demonstrated. The second form of the disease occurs as a rule in hogs that are immunized several months previously against

erysipelas. Anatomically, a hyaline thrombosis of almost every blood vessel in the diseased skin is the most striking feature. The cutaneous necrosis represents an allergic reaction due to the combined action of antigen and antibody.

C. ALEXANDER HELLWIG.

POSTMORTEM OBSERVATIONS ON INFANTS WHO DIED IN LÜBECK AFTER IMMUNIZATION AGAINST TUBERCULOSIS. P. SCHUERMANN, Verhandl. d. deutsch. path. Gesellsch. **26**:265, 1931.

The anatomic examination of fifty infants post mortem revealed that as a result of oral infection primary tuberculous lesions may be present in any organ that can be reached from the mouth. Only in eleven infants was the primary lesion found in a single organ, the small intestine, while in all the others primary lesions were present at the same time in two or more organs (small intestine, region of the neck, middle portion of the digestive tract, lung). Except in the small intestine, the primary lesion was found most frequently in the tonsils and in the middle ear. As infections in unusual locations were observed: primary tuberculosis of the duodenum, stomach and esophagus and apparently secondary tuberculosis of the larynx and of a dental follicle. The duration of the disease in the fifty infants varied between nine and thirty-four weeks. The causes of death were meningitis, inanition, intestinal obstruction and some rarer complications. Not infrequently, a nonspecific acute or subacute interstitial hepatitis was observed.

C. ALEXANDER HELLWIG.

THE RELATION OF THE NUMBER OF TUBERCLE BACILLI TO THE LESION. A. SCHMINCKE and SANTO, Verhandl. d. deutsch. path. Gesellsch. **26**:275, 1931.

Intracorneal and subcutaneous injections of different amounts of tubercle bacilli were given to rabbits, and it was found that the severity of the primary lesion ran parallel to the number of injected organisms. The secondary lesions, however, in the regional lymph glands, were without relation to the number of infecting tubercle bacilli, but were always maximal reactions. Systematic histologic and bacteriologic examinations of tuberculous lesions in human lungs showed that the severity of the tuberculous process does not depend on the quantity of the infecting organisms. In acute forms of pulmonary tuberculosis small amounts of organisms may be found, and, on the other hand, large numbers of tubercle bacilli may be present in chronic lesions. The deciding factor in the morphology of the tuberculous process is apparently the individual resistance against tubercle bacilli, whether congenital or required.

C. ALEXANDER HELLWIG.

## Tumors

AN EMBRYONIC TUMOUR OF THE KIDNEY IN FOETUS. G. W. NICHOLSON, J. Path. & Bact. **34**:711, 1931.

This is an account of a single case, with a comparison with physiologic development. I use the name "embryonic tumor" instead of "mixed tumor" or "adenosarcoma," as it accentuates the most characteristic morphologic feature of the tumor: It mimics or, as I try to show, retains the structure (and functions) of the developing kidney with a surprising degree of accuracy, in general outline and in detail. It is an interesting fact, used to the present day as an argument for the "congenital" origin of tumors in general, that the specimen, like others of its kind, was present at birth. It is therefore congenital and embryonic in every sense. And it is true that by far the greater majority of these tumors are observed in the first years of life. But birth is a mere incident in the life of the individual. It introduces him to a new environment to which he must adapt himself: his physiologic reactions are modified and evoked, but no new reactions are acquired. Does not this argument apply with equal force to his reactions to

an abnormal, or accidental, environment inside and outside the uterus? I see these embryonic tumors of the kidneys having their chief importance for oncology, not as congenital new growths, but as developmental malformations: they represent the physiologic evolution of a somatic tissue after abnormal stimulation at a time when growth is active and differentiation begins. They differ from the developing organ in that growth continues, and differentiation is aborted. The tumor, as I conceive it, does not arise in a malformed organ, but represents—and is—the malformed organ. Paul (1886) very rightly observed that "a normal tissue is just as congenital as a rudiment" or cell rest. Every tumor—like every physiologic organ—is truly congenital and truly acquired, whether it arises in an embryo as a reaction to an unknown stimulus or in a centenarian as a reaction to x-rays, soot, tar or what not. For the reaction is innate in either case, and therefore congenital and entirely physiologic; the stimulus alone is extraneous to the reacting part, acquired and pathologic. This is the plain teaching of pathology—free from theory—as I understand it.

AUTHOR'S SUMMARY.

THE ANTI-CARCINOGENIC ACTION OF DICHLORODIETHYLSULPHIDE (MUSTARD GAS). I. BERENBLUM, J. Path. & Bact. **34**:731, 1931.

The inhibition of the induction of warts that results when mustard gas is added to a carcinogenic tar is due to some local action of the mustard gas on the tissues, causing the latter to become refractory to the carcinogenic action of the tar. This refractory state develops almost as soon as the mustard gas treatment is begun, and subsides soon after this treatment is discontinued. While the induction of a wart is inhibited, neither the preliminary hyperplasia of the epithelium nor the subsequent growth of the wart is in any way interfered with, when mustard gas is allowed to act on the skin. In brief, therefore, the inhibitory effect is a process, strictly limited in extent and time of action, which interferes with the induction of a wart without influencing the epithelial changes that either precede or follow the actual induction of the wart. Though it has been possible to produce a simple wart in one mouse as a result of repeated application of a 0.05 per cent solution of mustard gas in liquid paraffin, it is doubtful whether mustard gas can be safely considered as a carcinogenic agent. While the earlier experiments were in keeping with the view that the inhibition was due merely to the production of a superoptimal degree of irritation, subsequent experiments have failed to support this hypothesis. It becomes necessary, therefore, to consider whether the inhibition is after all due to some specific chemical action of mustard gas on the tissues. The fact that mustard gas can inhibit the induction of tar warts without interfering with the early epithelial hyperplasia suggests that no parallel can be drawn between the amount of hyperplasia produced by an irritant and the carcinogenicity of that irritant.

AUTHOR'S SUMMARY.

RETICULUM CELL CARCINOMA OF THE THYMUS. S. MCDONALD, JR., J. Path. & Bact. **35**:1, 1932.

A locally malignant reticulum cell carcinoma of the thymus gland in a man, aged 59, is described. It is suggested that the neoplasm originated in a portion of involuted thymic tissue.

AUTHOR'S SUMMARY.

MITOSIS IN THE HEPATIC METASTASES OF MALIGNANT TUMORS. R. A. WILLIS, J. Path. & Bact. **35**:11, 1932.

A simple and reliable technic for the postmortem enumeration of the proportion of the cells in mitosis in malignant tumors is described. Nine tumors of various nature and origin and their hepatic metastases have been examined. In all, the mitotic activity of the hepatic deposits decidedly exceed that of the primary growths. Evidence is advanced in support of the view that hepatic tissue is a

highly favorable medium for the growth of most kinds of malignant cells, and it is suggested that this may be related to the high carbohydrate content and low arterial vascularity of the liver.

AUTHOR'S SUMMARY.

PLASMACYTOMA OF THE NASOPHARYNX. J. W. S. BLACKLOCK and C. MACARTNEY, J. Path. & Bact. **35**:69, 1932.

The case described is one of multiple small, plasma cell tumors occurring in the nasopharynx of a man, aged 64.

AUTHORS' SUMMARY.

PRIMARY CARCINOMA OF THE LUNG. E. PEKELIS, Tumori **5**:33, 1931.

This article compares the statistics of the various institutes of pathology in Italy and in foreign countries, describes the gross and microscopic picture of pulmonary carcinoma, and discusses the possible etiologic factors in the production of the disease. Five cases of pulmonary carcinoma are described. Three of these were bronchial adenocarcinoma, one was a diffuse infiltrative carcinoma, and one was a papillomatous carcinoma. In all of the cases, the new growth originated in the hilus, and macroscopically was of a nodular type.

G. PATRASSI.

THE SOLUBILITY OF CARCINOMA LIPOID IN SERUM. R. WILLHEIM and K. STERN, Biochem. Ztschr. **239**:473, 1931.

The authors attempt to substitute for the unreliable method of cell counts in the test for carcinolysis (Freund and Kaminer) the measurement of the solubility of carcinoma lipoids. They found that normal serum can dissolve carcinoma lipoids. The amounts of lipoid dissolved increase with increasing amounts of normal serum. Carcinoma serum, on the other hand, gives off its own lipoids to the carcinoma lipoids used. The lipoids were extracted from carcinoma cells freed from adherent connective tissue and detritus. They are unstable and show marked differences in sensitivity in regard to the reaction described. Fractioning of the lipoids did not give better results.

WILHELM C. HUEPER.

EXPERIMENTAL CHANGES IN THE SERUM REACTION TOWARD CARCINOMA CELLS. R. WILLHEIM and K. STERN, Biochem. Ztschr. **239**:484, 1931.

Human carcinoma cells were injected intraperitoneally and solutions of carcinoma lipoids intravenously into rabbits. They showed then the same curves of lipoid solubility as carriers of human carcinoma. Control examinations with normal cells and lipoids yielded negative results. The immunologic aspect of these findings in regard to susceptibility to carcinoma is discussed.

WILHELM C. HUEPER.

MALIGNANT RHABDOMYOMA OF THE PROSTATE GLAND IN A CHILD. K. KATZMANN, Frankfurt. Ztschr. f. Path. **41**:297, 1931.

Such a tumor is reported in a 13 months old child. Grossly, it was of the size of a hazelnut and of very firm consistency, and protruded into the urinary bladder. It had led to a compression of the mouth of the urethra. There also was found a cystopyelitis. Histologically, the tumor consisted of transversely striated muscle fibers, with many cells. The cells had many nuclei, were rich in chromatin and showed several nucleoli. In addition to the transverse striations, a longitudinal striation of the fibers was occasionally observed. An invasion of the blood vessels by the muscle elements was often found. Thirteen cases of rhabdomyoma of the prostate gland reported in the literature are also briefly discussed.

O. SAPHIR.

THE BLOOD OF PATIENTS WITH CANCER. G. CREUZBERG, F. DANNMEYER, O. HARTLEB, E. L. LEDERER, L. VON NOEL, J. SCHUBERT, H. SEEL and L. TREPLIN, Strahlentherapie **42**:609, 1931.

Von Noel, from studies made on the ether-soluble (and presumably lipoid) extracts of blood serums of cancerous and noncancerous persons, shows differences between the two. In cancer, the fatty acids of the blood are preponderately of low molecular weight. There are also differences in the values of saponification, free fatty acid, neutral fats and unsaponifiable material. These data are utilized by von Noel in the construction of a cancer number (Krebszahl), its magnitude being indicative of the presence or the absence of cancer.

Dannmeyer, Hartleb and Schubert call attention to the differences in the absorption spectra from cancerous and noncancerous persons. They consider these differences sufficiently constant to be of diagnostic value.

Lederer measured the ability of various samples of blood serum to inhibit the sedimentation of colloidally dispersed Berlin blue. Serum from noncancerous persons, would, in greater dilution, exert a protective colloid action on this dye, than would the serum from the blood of cancerous persons. The investigator considers this as of some diagnostic importance.

Creuzberg and Seelin tested the therapeutic effects of injections of (1) extracts of cancerous serum, prepared by von Noel, (2) extracts of noncancerous serum and (3) furosaccharate (? probably furfural or methyl furfural) in conjunction with ultraviolet irradiation on tumor-bearing mice. The first were without effect, but the second and third inhibited the growth of the tumors.

Treplin considers the cancer number of von Noel and the spectroscopic picture of Dannmeyer and Hartleb as of more diagnostic significance than the Lederer sedimentation test.

## Medicolegal Pathology

INCIDENCE AND SITUATION OF MYOCARDIAL INFARCTION. A. R. BARNES and R. G. BALL, Am. J. M. Sc. **183**:215, 1932.

One thousand consecutive, nonselected postmortem examinations are reviewed. In forty-nine cases (4.9 per cent) the examination showed myocardial infarction. In twelve of these the infarcts were multiple. The left anterior descending branch of the left coronary artery was involved in twenty-eight cases; the circumflex branch of the left coronary artery, in seventeen cases, and the right coronary artery, in twenty cases.

WILLIAM FREEMAN.

OCCUPATIONAL MELANOSIS. L. M. WIEDER, Arch. Dermat. & Syph. **25**:624, 1932.

Wieder reviews the literature and presents the case of a 37 year old white chemist who handled finished dyes, naphthalene acids and vat dye intermediates. Within four years a dermatitis developed, in which melanosis of the face and neck was the most prominent symptom. Biopsy of the lesion revealed intracellular edema of the epidermis and moderate follicular hyperkeratosis with considerable pigmentary activity in the basal layer of cells. Melanoblasts were abundant along the basal layer, and chromatophores with much pigment were numerous in the superficial dermis. Vacuolization of the melanoblasts produced a pseudo-edematous appearance at the dermo-epidermal junction. There was also moderate pigmentation in the malpighian layer. No vascular or connective tissue changes were found.

WILLIAM FREEMAN.

HYDROCYANIC ACID GAS POISONING BY ABSORPTION THROUGH THE SKIN. P. DRINKER, J. Indust. Hyg. **14**:1, 1932.

Drinker reviews the literature indicating that hydrocyanic acid gas may be absorbed through the skin of animals and human beings, thereby leading to poisoning and possibly death.

WILLIAM FREEMAN.

SUDDEN DEATH FOLLOWING CISTERNAL PUNCTURE. B. C. RUSSUM and M. W. BARRY, Nebraska State M. J. **17**:30, 1932.

The authors review the literature and report two cases in which death followed cisternal puncture. In both instances (involving 4 months old girls) death was caused by hemorrhage brought on by the puncture. In both instances, the pial vessels were punctured.

WILLIAM FREEMAN.

SPONTANEOUS RUPTURE OF THE HEART. F. R. BARNES, New England J. Med. **206**:631, 1932.

A 50 year old white man suddenly collapsed and died, receiving a laceration of his forehead in hitting a stove. He had previously complained of severe pain in the left arm and chest. Death was instantaneous. Postmortem examination revealed a perforating laceration of the left ventricular myocardium, 1 inch (2.5 cm.) upward from the apex. The literature of such a condition is reviewed from a statistical basis.

WILLIAM FREEMAN.

A CASE OF ACUTE YELLOW ATROPHY OF THE LIVER DUE TO CINCHOPHEN. S. C. LIND, Ohio State M. J. **28**:28, 1932.

A case of acute yellow atrophy of the liver due to ingestion of 90 grains (5.8 Gm.) of cinchophen is recorded. The patient lived two and one-half months following the administration of the drug.

WILLIAM FREEMAN.

TRAUMATIC APPENDICITIS. L. MILSON, Wisconsin M. J. **31**:100, 1932.

Milson reports the case of a man, 19 years of age, in excellent health, who was struck in the abdomen by an automobile traveling at a fairly rapid rate of speed. A sharp abdominal pain with nausea set in immediately after the injury. All of the signs and symptoms of acute appendicitis developed. Operation revealed an acutely inflamed appendix with a large fecalith obstructing the lumen and protruding through the appendiceal mucosa into, but not through, the submucosa. No other abdominal viscera were apparently injured. Milson believes that severe injuries to the abdomen may play a part in the etiology of acute appendicitis.

WILLIAM FREEMAN.

SUDDEN DEATH FROM SHOCK IN ATTEMPTED ABORTION. M. DUFOUR, Ann. de méd. lég. **12**:7, 1932.

A girl, 16 years of age, had a cannula introduced into the vagina so that water could be forced into the uterine cavity. The patient died soon after the cannula was inserted. All of the organs were found normal at autopsy except for excoriations and erosions of the cervix. The embryo was intact. The conclusion by the author is that sudden death was due to shock during an attempted abortion.

H. S. THATCHER.

EXHUMATION OF NEW-BORN INFANTS. G. STRASSMANN, Beitr. z. gerichtl. Med. **11**:36, 1931.

Strassmann believes that autopsies on exhumed new-born infants may occasionally reveal whether or not the infant lived and whether it died from birth trauma or from natural causes. The Gram-Weigert and sudan stains are especially valuable in demonstrating inhaled amniotic fluid.

O. SAPHIR.

IMPORTANCE OF MEDICOLEGAL EXPERT AT THE SCENE OF CRIME. ZANGGER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:101, 1931.

In the realm of legal medicine belongs not only the study of the medical phases encountered, but also, and mainly, the logical correlation of all the facts present on the premises of crime or accident. The action of a force or violence that caused injury to or destruction of the human body, and also characteristic damages to the surrounding objects, must be accurately analyzed and their mutual relations considered and evaluated with the accompanying circumstances, in order to arrive at and to express a scientifically correct opinion of all the happenings. A biologiomedically and medicolegally trained observer, with his background of sound scientific knowledge can render valuable service in gathering conclusive evidence at the scene of crime. In a trial, the testimony of lay witnesses as to their observations may be inaccurate and misleading, and conclusions arrived at from their findings may be erroneous and deceiving, but the expertly gathered, scientifically analyzed and convincingly introduced proof of facts will clear up the apparent inconsistencies and discrepancies and lead to justice.

E. L. MILOSLAVICH.

THE MEDICOLEGAL AUTOPSY FROM A CRIMINALISTIC STANDPOINT. NIPPE, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:103, 1931.

The purpose of the medicolegal autopsy is not only to detect and register the pathologic changes, damages and injuries present and to establish the cause of death, but to determine a likely fault, guilt or crime. From the anatomic character of a wound, one can occasionally conclude what type of weapon was used. Presence of foreign bodies in a wound, for instance, minute particles or parts of an instrument, such as fragments of a knife, razor, glass splinters from a bottle or jar, etc., may serve to identify the weapon and its owner. The larger fragments are easily removed from the bed of the wound or the canal with forceps, or the entire wounded area may be excised, minutely washed and shaken, and the sediment centrifugated. Unforeseen, important findings may be obtained. Examination of urine for albumin is of certain practical value only when one critically considers the microscopic picture of the kidneys, since cadaveric desquamation of the epithelial elements of the bladder and autolytic processes may lead one to incorrect conclusions as to the presence of albumin. Sugar may be unexpectedly detected in the urine of persons who died following acute lesions of the brain, as hemorrhages, while a previous clinical examination, prior to the injury to the brain, was negative. The urinary bladder rarely shows postmortem contraction. The uterus exhibits a similar behavior following miscarriage or delivery. The uterus, for instance, presents a peculiar resistance to putrefactive processes. The rigor mortis of the heart and the fragmentation of the myocardial fibers are quite reliable signs of the functional power and activity of the heart. In exhumed, unembalmed bodies, the intestinal canal is usually found better preserved than the parenchymatous organs. Later on after death the consistency of the contents of the large intestines may change; one may observe either liquefaction or inspissation of the fecal material. In examining the hair, one may detect important findings as to cut surface — changes due to burns, injuries by blunt force, by instruments, by automobile impact or by electric currents, gunshot effects, etc. The cadaveric hypostasis, even in cases of lethal hemorrhages, may appear after one-half hour or three quarters of an hour, and up to four hours after death the change in the position of the body will result in a change in the location of the hypostatic areas. The cadaveric rigidity starts, as a rule, three quarters of an hour after death, in the jaw, and after from one and one-half hours to two hours it is well pronounced in the extremities. After it disappears it may spontaneously reappear, and a revolver placed in the hand of a dead person may later be found grasped firmly by the rigid hand. This phenomenon may lead to misinterpretation with respect to suicide. About twelve hours after death the rigidity is complete, if the body has been in a cool environment. If the rigor mortis was artificially loosened, it

does not recur; otherwise, it disappears on account of autolytic processes or decomposition. Should the body be kept in a cool place, the rigor mortis may persist for many weeks and directly pass into desiccation and mummification of the corpse. In cases of gunshot wounds, one should never omit an accurate inspection of the clothing. If a pistol is discharged at a very close range, the powder gases may expand between the surface of the body and the clothing, for example the shirt, and produce a smudging of the skin and of the inner aspect of the shirt. Advancing putrefaction may obscure the characteristics of a shot fired at a close distance, but application of hydrogen peroxide solution may bring out the smudged areas. Microscopic examination of the canal of the wound may disclose presence of torn particles or fibers of fabric.

E. L. MILOSLAVICH.

SUDDEN DEATH FROM NATURAL CAUSES IN ADULTS. GUNTHER WEYRICH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:211, 1931.

A statistical analysis of 2,668 cases of sudden death discloses that in nearly half (42 per cent) the unexpected death occurred on account of disease of the circulatory apparatus, 550 cases showing coronary sclerosis, with predominance of males. Considering the males alone, in 47 per cent death resulted from cardiac or aortic diseases. The mortality was highest in the sixth decade of age. Of 623 instances of sudden death from diseases of the respiratory organs, 267 resulted from pneumonia and pleurisy, while pulmonary embolism was noted in 47 autopsies. The highest mortality was observed during the month of February, the lowest in August. While every fifth case of sudden death was due to coronary sclerosis, cerebral apoplexy was found in only every twentieth instance. This statistical fact is of great practical importance, since, in a case of unexpected sudden death, the average physician ordinarily assumes a hemorrhage of the brain. Three times death from paralysis of the heart occurred during sexual intercourse. Considering the relation between occupation and sudden death due to cardiac disease, this study reveals that mental workers are represented by an unusually high percentage as compared with persons engaged in heavy manual labor.

E. L. MILOSLAVICH.

PATHOLOGY OF SUDDEN DEATH FROM NATURAL CAUSES DURING COITUS. G. SCHRADER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:223, 1931.

In legal medicine, sudden death forms an important chapter, since often dubious circumstances surround the unexpected catastrophe. This is particularly true in instances of lethal collapse of an apparently healthy person during the sexual act. Three such cases are presented, each of peculiar criminalistic significance. The first case involved a man, 50 years of age, visiting a prostitute. The man was found moribund in her room, while she was apparently unconscious but rapidly recovered. A gas jet was open, and the odor of gas was noticeable. The autopsy disclosed syphilitic mesaortitis with thrombotic deposits and alcoholic intoxication, but no evidence of carbon monoxide poisoning. The prostitute, frightened by the sudden collapse of her companion, had tried to feign an accident. In the second case, a young sportsman died suddenly during sexual intercourse. The postmortem examination disclosed a large amount of blood in the subarachnoid space at the base of the brain, due to a hemorrhage from the posterior part of the basilar artery, which showed an old tear with an intramural hematoma. The latter lesion was explained as the result of an indirect trauma to the head sustained eight days prior to death owing to a fall while exercising. In the third case, a 27 year old woman suddenly expired during the first night of her honeymoon. At autopsy, syphilitic mesaortitis and stenosis of the coronary ostia were found. Thrombotic material was attached to the diseased ascending aorta and extended into the opening of the left coronary artery.

E. L. MILOSLAVICH.

ASPIRATION OF PARTICLES OF BRAIN INTO THE RESPIRATORY TRACT IN INJURY TO THE SKULL. D. HIDASSY, Orvosi hetil. **1**:92, 1931.

A boy, 9 years old, received a fatal fracture of the base of the skull from being run over by the wheel of a truck. At the autopsy there was found a considerable amount of brain tissue in the larynx and bronchi in addition to fluid blood.

## Technical

IMMEDIATE AND DIRECT METHODS OF TYPING PNEUMOCOCCI. R. R. ARMSTRONG, Brit. M. J. **1**:187, 1932, and W. R. LOGAN and J. T. SMEALL, ibid. **1**:189, 1932.

The procedure used by Armstrong is as follows: "A suitable fleck of sputum is selected. Three small samples of this are placed, equidistant, on a microscope slide, and numbered 1, 2 and 3. Each sample is emulsified with four times its volume of the corresponding diagnostic serum, the addition of serum and emulsification being conveniently performed with a platinum loop. Cover glasses are applied, and the slide is set aside for a few minutes while a further sample from the selected fleck of sputum is smeared on a slide, fixed by heat, and stained by Gram's method. The general bacterial flora of the sputum and the number of pneumococci present are apparent at a glance in the stained film, which exactly represents the characters of the sputum samples selected for the diagnostic test. It is of special value to be informed in advance of these characters, for if the pneumococci are plentiful, a positive result in the typing will be apparent at once; no time need be wasted in useless search, therefore, when, as in the case of a group IV infection, there is no reaction. The slide carrying the fresh emulsions of sputum and specific serums is now examined by means of a 4 ocular, one-sixth objective, and plane mirror, the condenser being removed. Whereas the unstained pneumococci, when present in small numbers, are but just visible in the case of a negative reaction, the result in the case of a positive reaction is a conspicuous increase in the size of the individual pneumococcus, due to conjugation of coccus and homologous antibody. The enlarged cocci have a characteristic ground-glass appearance, with a highly refractive peripheral zone. A positive reaction is at times appreciable to the naked eye on holding the preparation to the light. The positive, as compared with its companions on the same slide (which serve as controls), is seen to be opalescent, owing to the great increase in size of the "sensitized" cocci. When the pneumococci are thickly coated with seromucinous pneumonic secretion, the characteristic appearances develop more slowly as the specific serum soaks its way through. In such cases twenty minutes may elapse before full completion, although type may be distinguished much sooner by the change in those pairs that are floating free."

The technic used by Logan and Smeall for the direct typing of pneumococci is practically that described by Armstrong. An emulsion of the sputum is made with physiologic solution of sodium chloride. Four thin glass slides are marked I, II, III and control, and a large loopful of the undiluted type serum is placed on the appropriate slide, a drop of physiologic solution of sodium chloride being put on the control slide. The sputum emulsion is then taken up in a capillary pipet with a teat. A drop of the required size is placed beside each drop of serum and then mixed by tilting the slide backward and forward. Sometimes it is better to drop the emulsion on to the serum; in other cases, in which the consistency is more gelatinous, it is necessary to mix with a loop. A thin cover glass is placed on the mixture, which is then examined under the microscope. The authors use a one-twelfth oil-immersion lens, with the substage condenser racked down a little and the diaphragm closed to an extent that has to be constantly varied to get the best results. The plane mirror and a bright artificial light are employed. In cases in which pneumococci are present in large numbers, the swelling of the individual pneumococcus and the appearance of the dark line

sharply outlining the capsule, along with a darkening of the body of the pneumococcus itself — distinct from the whitish, sometimes almost greenish-white, capsular substance — are strikingly seen when the homologous serum has been used. In the other slides the pneumococci are seen to be much smaller, with a small halo, which is a little lighter in color than the surrounding sputum, but there is no dark line sharply defining the outline of the capsule. In specimens in which pneumococci are scanty it is sometimes only in the slide with the specific type-serum that they stand out and become recognizable, while, in specimens containing many streptococci in diplococcal form, again it is only the reaction to the specific serum that indicates which are pneumococci. With some specimens the test has to be performed several times before a successful result is obtained.

Intravenous Injection of Congo-Red in the Diagnosis of Amyloid Disease. J. E. Wallace, Lancet **1**:391, 1932.

Amyloid material absorbs congo-red. If an aqueous solution is injected intravenously, the decrease of the dye in the plasma or serum may be estimated colorimetrically; normally from 10 to 30 per cent disappears in one hour, but in amyloid disease the disappearance is much more rapid.

Autopsy Technic for Examining Nasal Sinuses and the Cerebellum. A. Schmincke, Centralbl. f. allg. Path. u. path. Anat. **53**:273, 1932.

The skin incisions employed in this method are carried across the shoulders from the outermost ends of the usual infraclavicular cuts and meet in the midline between the shoulders. Two flaps are then formed by a cut upward from this junction to the nape of the neck. After freeing the skin from the subcutaneous tissues, the mandible is disarticulated, and by chiseling through the maxillae the sinuses can be exposed. Reflection of the skin from the neck forward and upward allows exposure of the cranium for the usual cut in the greatest horizontal diameter for removal of the brain. When it is desirable to remove the brain and spinal cord in one piece, the two additional saw-cuts are made through the base of the cranium to the edges of the foramen magnum. Schmincke advocates this method for the demonstration of tumors of the cerebellopontile angle. Restoration of the body is simplified if the skin sutures are begun at the angle between the shoulders.

George Rukstinat.

The Serologic Diagnosis of Syphilis with the Citochol Reaction of Sachs-Witebsky. S. L. Schirwindt and A. V. Alekseeva, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:54, 1931.

The reaction was compared with the Wassermann and Kahn reactions and with the lentochol-reaction of Sachs-Georgi. It was proved superior to the lentochol-reaction; it was somewhat less sensitive than the Wassermann and Kahn reactions in the early stages of syphilis, in mixed chancre and in congenital syphilis, but almost equally sensitive in all other forms of syphilis. A tendency toward nonspecific positive reactions was observed. The results with cerebrospinal fluid, which were unsatisfactory with the original method, improved after cholesterol was added to the antigen and improved still more after precipitation of the globulin according to the procedure of Kahn.

I. Davidsohn.

Blood Cultures of Tubercle Bacilli According to Löwenstein's Method. Unverricht and S. Dosquet, Ztschr. f. Tuberk. **63**:338, 1932, and N. B. Oekonomopoulo, B. Papanikolaou and G. Joannides, ibid. **63**:340, 1932.

In both these articles essentially negative results are reported from cultivating the blood for tubercle bacilli according to the method described by Löwenstein.

# Society Transactions

## NEW YORK PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, March 24, 1932*

PAUL KLEMPERER, *President, in the Chair*

### A CASE OF MALIGNANT CARCINOID OF THE ILEUM. LOUISE H. MEEKER.

The patient, 61 years old, was admitted to the hospital because of abdominal cramps. The past history showed attacks of cramps relieved by cathartics. The preoperative diagnosis was intestinal obstruction. At operation, kinking of the intestine with dilatation above was found, and resection of about 3 feet (91 cm.) of the lower part of the ileum was done.

The gross specimen was a portion of the small intestine, 550 mm. in length. The mesentery was contracted so as to produce sharp kinking of the bowel, and in the mesentery there were opaque, somewhat yellow thickenings. When the intestine was opened, the mucous membrane presented numerous hemorrhagic spots and at one place a large area of extravasated blood. Here the wall of the intestine was distended to form a pouch about 50 mm. in diameter. In the lumen there was considerable mucus stained by bile.

Microscopic sections through the firm portions in the mesentery at the point of kinking of the intestine showed a dense fibrous stroma, in which there were many irregular nests of deeply staining cells. These cells had slightly vesicular, round nuclei, uniform in size, and a small amount of cytoplasm. Some of them resembled lymphocytes. They were grouped in well defined nests, and within these nests the epithelial cells were occasionally arranged around a circular lumen, indicating a tendency to form a gland duct. Mitotic figures were not recognized. The cell nests were intimately associated with numerous large nerve trunks. The neoplastic epithelium extended beyond the intestinal wall into the mesentery and invaded several lymph nodes.

The final diagnosis was "malignant neurocarcinoma," based on (1) the chromaffin color of portions of the gross tumor; (2) the typical rosette formations, each about a cavity containing colloid-like material, and lack of mitotic figures; (3) the proliferation in relation to the nerves, and (4) the metastases of the tumor to the lymph nodes.

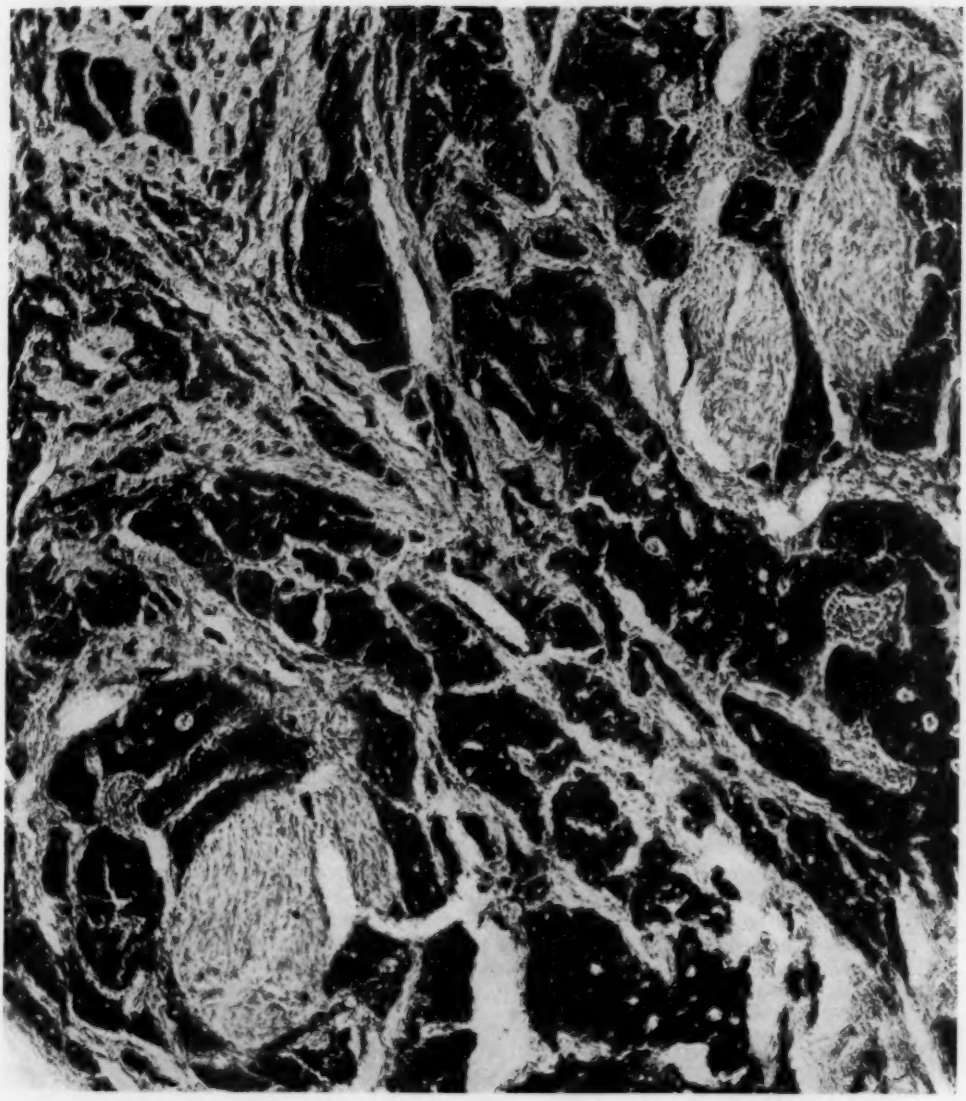
The lack of union with glands of the intestinal mucosa may be explained, according to Masson, by former epithelial buds sending isolated cells into the nerve tissue.

### ACTINOMYCOSIS OF THE BRONCHI AND LIVER. CHARLES T. OLCOTT.

A specimen of an abscess of the liver occurring in association with bronchiectasis of the lower part of the right lung was presented. Actinomycetes were found both in the lung and in a solitary abscess in the upper surface of the liver. Although there was a history of a mass in the cecal region two years before, no remnant of this was found at autopsy.

### ACTINOMYCOSIS OF THE MESENTERY OF THE COLON. CHARLES T. OLCOTT.

A lantern slide of a surgical specimen obtained by Dr. John H. Garlock was shown. A woman, aged 53, showed symptoms of obstruction in the transverse colon. Resection showed no lesions in the intestine itself, but actinomycetes were



Microscopic appearance of the carcinoid of the ileum in Dr. Meeker's case. The masses of tumor cells show small lumina. The light areas are nerve trunks.

found in a hemorrhagic area of the mesentery. Resection was followed by a cure of two and a half years' duration.

DISCUSSION

ALFRED PLAUT: In regard to the last case, may I make somewhat pessimistic remarks? I, too, once thought that I had seen a cure in a case of abdominal actinomycosis. I followed the patient for five and a half years, during which time she remained well, but I finally heard that she had retired to the parental farm and had died of an unknown disease. There was no autopsy, but it is reasonable to presume that she died of an actinomycotic process. I do not know of any permanent cure of actinomycosis. Actinomycosis is a much more frequent disease than we think. Many years ago a surgeon came to me about a case, and said that he felt sure it must be actinomycosis, but that he had gone to many pathologists and bacteriologists and had got no help. He asked if I could help him, and I said, "Probably not," but I finally found one granule, just as Dr. Olcott mentioned, and I am sure that if we had not had the time to make such tedious examinations, the one granule would have been missed, and the diagnosis with it.

AN UNUSUAL ADENOCARCINOMA OF THE STOMACH. EDWARD B. GREENSPAN.

A case of adenocarcinoma of the stomach in a 41 year old man was presented because of the remarkable resemblance of the tumor grossly and histologically to chorio-epithelioma.

The tumor grew from the posterior wall of the stomach near the pylorus, causing a large filling defect on the greater curvature. It was a mushroom-shaped, hemorrhagic tumor, measuring 5 by 5 by 2 cm. The regional lymph nodes revealed metastases. There were oval, hemorrhagic nodules in the liver, greatly resembling metastatic chorio-epithelioma. There was also carcinomatous lymphangitis of the pleura with nodules in the pleura and in the pulmonary parenchyma.

Microscopically, the remarkable resemblance of the metastatic nodules in the liver to chorio-epithelioma was noted. Large, multinucleated giant cells, suggestive of syncytial cells, and oval cells with pale, vesicular nuclei, resembling Langhans' cells, made up the tumor. Here and there were lakes of blood surrounded entirely by tumor tissue. A section through the tumor of the stomach revealed nests of cells showing frequent mitoses, arranged in the distinct pseudoglandular formation of adenocarcinoma, replacing a part of the mucosa. Here, as in the liver, one saw in the submucosa collections of cells resembling syncytial cells and Langhans' cells of the placenta, often surrounding collections of blood, and invading the muscular layers and at one point the muscularis.

In 1905, Davidsohn reported a case in which histologic examination of one portion of the tumor revealed great similarity to chorio-epithelioma, while in other portions definite carcinoma was seen. He believed that he was dealing with two separate tumors. In 1907, Helmholtz published a description of a tumor of the stomach, which he labeled "A Syncytiomatous Tumor of the Stomach," and which he suggested was the result of a misplaced "anlage."

ISOLATED NECROTIZING ARTERITIS AND SUBACUTE GLOMERULONEPHRITIS IN A CASE OF GONOCOCCAL ENDOCARDITIS. MILTON HELPERN and MAX TRUBEK.

In a case of subacute glomerulonephritis of ten weeks' duration, death occurred from uremia with pericarditis. The illness developed eight weeks after gonorrheal urethritis, complicated by gonococcic ophthalmia. At necropsy, right-sided subacute gonococcic endocarditis of the pulmonic valve and typical subacute glomerulonephritis were found.

In addition, isolated necrotizing inflammatory lesions of the small arteries were found in the choroid coat of the eye and in the testicle. These vascular lesions

exhibited many of the morphologic features of periarteritis nodosa and were considered as belonging to that group. The larger arteries of the body were not involved, and the distribution of the lesions was not extensive enough to produce clinical manifestations.

The renal lesion is interpreted as a severe reaction to the toxin produced by the gonococci growing on the pulmonic valve. The vascular lesions, which in this case were anatomically dissociated from the kidney, were also considered to be a specific reaction to the same toxin.

The findings strengthen the conception that these vascular lesions and those of periarteritis nodosa do not represent a specific disease, but rather a reaction of the blood vessels to any of a whole group of toxins.

DISCUSSION

MAX TRUBEK: Gruber maintains that periarteritis nodosa may be caused by any one of a number of infections, identical arterial lesions occurring in the previously sensitized vessels. The preceding infection need not be a severe one—coryza, suppurating wounds, furuncles, sore throat, rheumatic fever, erysipelas, syphilis, gonorrhea and other conditions. His surmise as to the gonococcus seems proved in our case. The relatively low virulence of the gonococcus—judging from the long duration of the infection—furnished conditions for sepsis lenta, which Siegmund considered of importance in his case of streptococcic endocarditis associated with periarteritis nodosa.

We believe that in our patient the general infection by gonococci with endocarditis existed when the patient was being treated for the gonococcic ophthalmitis.

The evidence for a specific infection as the cause of periarteritis nodosa has been more or less in dispute. The positive results of von Hann and of Harris and Friedrich have kept the question open. Arkin accepted the virus theory without further proof. Otani obtained negative results, repeating the experiments of von Hann and using tissue and blood from a typical case of the disease for his animal inoculations.

The glomerular disease in our case was present without any arterial lesion. Renal complications in periarteritis nodosa may be purely arterial, purely glomerular or both. In our case, the glomerular nephritis was caused by the gonococcic toxemia. The periarteritis nodosa was an isolated occurrence, not the systemic disease.

Lesions in the eye in this disease have been previously described. The ophthalmoscopic changes are usually recorded as albuminuric retinitis. In our case, the retinal picture showed papilledema and hemorrhage.

Müller and Christeller mention lesions in the choroid in their cases. Böck and Herrenschwand demonstrated lesions in the extra-ocular muscles, central artery of the retina and ciliary arteries, respectively. Goldstein and Wexler showed a case with choroid involvement not unlike that in our case.

Lesions of the testis have been described a number of times, the involvement occasionally producing infarction and necrosis when both sets of vessels are affected.

Isolated lesions are not unusual. At times, characteristic changes occurring in only a few organs have been described. This fact may depend on the variety and number of the sections selected.

Microscopic identification of the disease, previously unsuspected, has been a frequent occurrence.

ISADORE GOLDSTEIN: Dr. Wexler and I studied three cases of periarteritis nodosa. We saw two of the patients during life. The patient whose case was reported by us was not seen during life. In one case there was bilateral papilledema with periarteritis in the other organs, but there was no periarteritis in the eye. In the case of the other patient whom I saw during life, I made a diagnosis of the malignant phase of essential hypertension. This was incorrect, for the man died of periarteritis nodosa. In that case there was no periarteritic lesion in the eye, while such lesions were present in some of the other organs. The case

reported by us was that of a woman, aged 19. There were microscopic lesions in the organs. In the eye, the iris, ciliary body and retina were normal, but the choroid disclosed lesions similar to those shown tonight. In the arteries we found either organized blood clots or fibrin, with marked proliferation of the endothelial cells and hyperplasia of the subendothelial tissue, consisting mostly of polyhedral cells. I think we were the first to call attention to this type of cell. We also drew attention to the sharply defined and thin media. There was necrosis of the arterial wall with marked infiltration of the adventitia and periadventitial tissue by lymphocytic cells. The same type of cell was found in the other organs. Mention was also made of the giant chromatophores, which showed so nicely in the case presented.

I do not believe that there is a typical picture of periarteritis nodosa of the fundus. Most of the cases are of the hypertensive neuroretinitis type, but the lesion shown here this evening apparently gives no fundus picture. If anything, this lesion should appear as a white spot, but we didn't see it, although our patient was studied during life, but not by one of us; so the question is still open whether periarteritis nodosa has a definite fundus picture.

ALFRED PLAUT: I would like to ask whether the authors are correct in calling the interesting lesions just presented periarteritis nodosa. I think not. The large amount of necrotic or fibrinoid change in the walls of the vessels, together with the small amount of inflammatory cellular reaction surrounding them, constitutes such a difference from the ordinary picture of periarteritis nodosa that I would rather call it necrotizing arteritis, and would not include it in the picture of periarteritis nodosa. I feel that twenty or thirty years from now the chapters on diseases of the arteries in our textbooks will be written differently. I do not know why the pathology of the arteries has been neglected so much, except for the chapters on arteriosclerosis and syphilis. More and more observations on peculiar lesions in arteries, which cannot be classified well, are coming into the literature. I feel that this is an important contribution to this chapter, most of which will be rewritten in the future, and I should not be astonished if twenty years from now many lesions that were previously listed under periarteritis nodosa are reclassified.

SOME PROBLEMS IN MEDICAL MYCOLOGY. J. G. HOPKINS.

The study of mycotic infections presents many problems of interest to the pathologist and the mycologist, which may be grouped under the following headings:

*Problems of Identification.*—The imperfect descriptions frequently given of fungi found in human infections make the classification of many such parasites extremely uncertain. The difficulty is partly inherent in their rudimentary morphologic state, which seldom presents characteristic structures by which they may be identified. Moreover, their morphologic characteristics in culture often bear no resemblance to those noted in the lesions. They vary in appearance when grown on different mediums, and, as Emmons has observed, variations that seem to be permanent develop in pure line strains. A clearing up of the confusion in regard to them demands that they be studied both by botanic and by bacteriologic methods. In studies of strains of Monilia morphologic descriptions combined with the results of immunologic tests have done much to clear up the confusion in regard to classification.

*Problems in Etiology.*—Infection with some fungi, such as Actinomyces and Sporothrix, apparently results from inoculation with the organism from some source outside the body. A search for reservoirs of infection in animals, in plants and in the soil is necessary to explain the etiology of these diseases and to control their spread.

*Problems in Infectivity.*—Some fungi are pathogenic under experimental conditions, reproducing in the laboratory the picture of the spontaneous disease. Others, such as Actinomyces bovis, are practically nonvirulent when experimentally

inoculated, and a study of the conditions under which they may produce lesions is essential to an understanding of these infections.

*Problems in Sensitization.*—The pathogenicity of some of these parasites in spite of their lack of virulence is explained by the fact that their hosts become sensitized to them. Studies in sensitization have already thrown much light on eruptions of the skin associated with dermatophytosis. Similar sensitization reactions occur in association with infections by monilia. Asthma is in some cases due to sensitization to fungi in dust, and there is evidence to show that certain cases of eczema are due to similar allergic reactions.

CLASSIFICATION OF YEASTLIKE PARASITES. RHODA W. BENHAM.

A definite classification of the yeastlike parasites is not possible due to the lack of knowledge as to the complete life history of these forms. However, some definite criteria for recognizing the types isolated from the various lesions and a uniform terminology need to be established. The names, Blastomyces, Cryptococcus, Oidium, Monilia, Saccharomyces and Torula have been used indiscriminately for a number of different organisms. Yeastlike organisms are found in deep-seated lesions of the skin, systemic infections, infections of the nervous system and superficial cutaneous lesions. A brief description of the organisms as seen in the lesions and as cultured from the more important of these diseases follows:

*American Blastomycosis* (Gilchrist, 1894).—In the lesion, the organism appears as a round, thick-walled, budding cell; in culture, as a filamentous form producing a white, fluffy colony—Blastomycoides dermatitidis.

*Coccidioidal Granuloma* (Wernicke, 1892).—In the lesion, the parasite is a large, round, thick-walled cell filled with numerous bodies considered to be spores. No buds are seen. In culture, the appearances are similar—Blastomycoides immitis.

*Chromoblastomycosis* (Pedroso, 1913).—Round, budding cells are seen in the lesion. The culture shows as dark brown or greenish, woolly growth—Phialophera verrucosa.

*Lymphangitis Epizootica* (Rivolta and Micellone, 1883).—The organism in the tissue appears as a small, oval body. No budding is shown. The culture is mycelial, resembling a faviform type of trichophyton—Cryptococcus farciminosus.

*European Blastomycosis* (Busse and Buschke, 1893).—Thick-walled, round cells are seen in tissue. The cultural growth is pasty. No mycelium and no ascospores are shown, only buds—Saccharomyces hominis.

*Torula Meningitis* (Stoddard and Cutler, 1916).—The torula appears in the lesion as a round, thick-walled, budding cell. The culture is yellow and mucilaginous. The organism is a round, budding cell, showing no mycelium and no ascospores—Torula histolytica.

There is also a meningitis due to a monilia-like organism (Ball, 1930).

*Superficial Cutaneous Lesions*—These include erosio interdigitalis (Kauffman-Wolff, 1914), chronic paronychia (Kumer, 1921), perlèche (Finnerud, 1929) and generalized dermatitis (White, 1929). In the lesions, the parasites are seen as budding cells and mycelium. The culture shows a pasty colony. Definite mycelium and moniliform clusters appear in corn-meal agar. Chlamydospores, large, thick-walled globular cells, are also seen. This morphology is characteristic of Monilia albicans. An identical species is found in thrush and sprue. It may be differentiated from other species of Monilia, Cryptococcus and Saccharomyces both by its morphologic aspects in corn-meal agar and by the agglutination reactions.

CLASSIFICATION OF DERMATOPHYTES. CHESTER W. EMMONS.

The classification of dermatophytes proposed by Sabouraud remains the most workable and the most widely accepted of those used. It is based primarily on the clinical aspects of the lesions. Having determined his genera and subgeneric groups in this manner, Sabouraud bases his specific characters largely on the

appearance of the giant colony. A natural classification based on the morphologic characters of the fungi would be desirable. Classifications proposed by Ota and Langeron, Guiart and Grigorakis, and others attempt such natural groupings. The attempts so far made are not satisfactory, because of the variations and intermediate spore forms that appear, and because of the dependence to some extent on quantitative rather than on qualitative differences.

Three series of variations appearing in three strains of dermatophytes are presented. In a strain of Achorion gypseum which arose from a single spore, six variants appeared in an old culture. They differ in microscopic and macroscopic characters from the parent strain and from each other sufficiently to deserve specific ranks according to the usual criteria. Shorter series of variations appeared in two strains of Trichophyton gypseum.

The dermatophytes appear to comprise a closely related group of fungi. It is hoped that a careful study of the characters held in common by different strains and of variations that appear in strains arising from single spores will aid in reducing the number of some of the imperfectly described "species" and contribute to a more satisfactory classification of these fungi.

DISCUSSION

PAUL KLEMPERER: Are the tissue reactions found in animals experimentally infected with pathogenic fungi in any way characteristic of or similar to the lesions provoked by the yeasts in the few cases that are seen in man? This question is asked particularly with reference to the one case that Dr. Hopkins referred to. This was a puzzling case for us, in which the histologic picture of the skin lesion did not in any way conform with the lesion that we learned to recognize as produced by yeast, in which the tubercle-like production is characteristic. I wonder if the reactions in animals are so variegated as those we see in human beings, or are they more uniform?

MAURICE RICHTER: I should like to ask whether morphologic variations in these organisms can be correlated with variations in virulence.

J. GARDNER HOPKINS: We have not been impressed in the few histologic specimens that we have had of sporotrichosis and blastomycosis with any characteristic tissue reaction. From the descriptions I have seen, I think it extremely difficult to make any other diagnosis than that of chronic granuloma.

CHESTER W. EMMONS: The strain of Achorion gypseum in which the longest series of variants appeared is not pathogenic for the guinea-pig, so that it was not possible to get a good series of inoculations, but in both strains of Trichophyton gypseum that showed the variants these were pathogenic for guinea-pigs, perhaps not quite so severely as the parent strains, but they produced definite lesions.

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## AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

C. PHILLIP MILLER, *Secretary*

*Nineteenth Annual Meeting, The University of Pennsylvania,*

*Philadelphia, April 28, 29 and 30, 1932*

SAMUEL R. HAYTHORN, *President, Presiding*

REGENERATION OF HEMOGLOBIN AS MODIFIED BY ABNORMAL CONDITIONS OF THE LIVER. F. S. ROBSCHEIT-ROBBINS and G. H. WHIPPLE, University of Rochester, School of Medicine and Dentistry.

A simple anemia was produced in dogs by withdrawal of blood. This anemia was maintained at a hemoglobin level of from 40 to 50 per cent for a period

of years. The hemoglobin output due to various diets was carefully evaluated and was constant as shown by repeated experiments during the entire period of the anemia.

With these observations as a base-line control, the regeneration of hemoglobin was determined under abnormal conditions of the liver, such as Eck fistula. Interesting differences have been noted in the reactions of the anemic dog with Eck fistula to standard dietary regimens. The liver in the dog with Eck fistula was further injured by chloroform and the regeneration of hemoglobin studied under these conditions.

PRODUCTION OF OSTEITIS FIBROSA WITH OVERDOSES OF VITAMIN D. ROBERT C. GRAUER (by invitation, introduced by Samuel R. Haythorn), Singer Memorial Laboratory, Pittsburgh.

Seven groups of adult guinea-pigs weighing about 500 Gm. were given viosterol in graded doses. The viosterol used was specially prepared so that 1 cc. of the oil contained 5 mg. of the activated sterol. The animals were kept on the regular laboratory ration of hay, leafy greens and white bread. The guinea-pigs were killed and examined at approximately seven day intervals, and sections were taken from the long tubular bones and from the costochondral junctions of the ribs. These were fixed in Zenker's fluid, decalcified and stained with phloxin and methylene blue (methylthionine chloride, U. S. P.).

No changes were noted in the guinea-pigs given doses under 10 mg. In the groups that received from 10 to 15 mg., bony changes were observed after the twenty-fifth day. There was lacunar resorption in the cortical portions of the long bones. These were lined by active osteoclasts. Endosteal fibrous proliferation with fibrous replacement of the decalcified bone was present. In the group that received 15 mg. of oil for thirty-six days there were areas of hemorrhage and resorption of the hemorrhagic areas with formation of cysts.

The costochondral junction of the ribs revealed thinning of the cortices, spontaneous fractures, fibrous ingrowths and the formation of osteoid tissue. The pictures presented were those of osteitis fibrosa cystica. Studies of the serum calcium, phosphorus and protein revealed only a slight increase over the established normal values.

AMMONIUM CHLORIDE OSTEOPOROSIS ON LOW AND HIGH CALCIUM INTAKES AT DIFFERENT AGES. HENRY L. JAFFE, AARON BODANSKY and J. P. CHANDLER (by invitation), the Hospital for Joint Diseases, New York.

Four litters of dogs, 3, 6, 8 and 18 months old, respectively, were used. Litter mates received a diet that in one case was high and in another low in calcium, with and without ammonium chloride. The diet consisted of fresh lean horse meat supplemented with bone meal and calcium lactate in the case of the dogs receiving the diet high in calcium, and with cod liver oil and tomato juice in all cases. The daily calcium supplement amounted to from 0.5 to 2.5 Gm. Once a week all dogs were fed cooked liver and kidney. The ammonium chloride, in 1 per cent solution, was given by stomach tube. At the end of the experiment as much as 1 Gm. per kilogram of body weight was given daily.

The animals were subjected to the experiment for eleven weeks. The bones in the controls on the diet high in calcium were normal in every respect. The controls on the diet low in calcium showed thinning of the bones.

In all age groups, the gradation of changes was found to be strikingly dependent on the intake of calcium. Dogs receiving a diet high in calcium plus ammonium chloride showed less osteoporosis than those receiving a diet low in calcium plus ammonium chloride or a diet low in calcium without ammonium chloride. In the younger age groups, the diet low in calcium plus ammonium chloride brought out more striking changes, including fractures and deformities, than the diet low in calcium without ammonium chloride.

BONE LESIONS IN RATS PRODUCED BY THE SUBSTITUTION OF BERYLLIUM FOR CALCIUM IN THE DIET. SHELDON A. JACOBSON (introduced by H. L. Jaffe), the Hospital for Joint Diseases, New York.

Experiments on the basis of the work of Branion, Guyatt and Kay were undertaken as follows: All animals except those of the first group received three drops of cod liver oil daily.

Young rats on the unsupplemented Steenbock diet became rachitic. A control group on the Steenbock diet plus cod liver oil had normal-appearing bones. On a calcium-free Steenbock diet, however, marked osteoporosis was manifest. When, for the calcium of the diet, beryllium was substituted, a lesion anatomically similar to marked rickets appeared. When, however, only one half of the calcium was replaced by beryllium, rickets at first appeared, but subsequently showed a tendency toward healing. There was some osteoporosis.

A straight meat diet brought about the appearance of severe osteoporosis. The addition of beryllium to this regimen resulted in a rachitoid lesion being superimposed on the osteoporotic condition of the bones. When both beryllium and calcium were administered, an initial rachitoid lesion developed, but subsequently resolved; the osteoporosis, however, remained.

THE REPAIR OF ARTICULAR CARTILAGE AND THE REACTION OF NORMAL JOINTS OF ADULT DOGS TO SURGICALLY CREATED DEFECTS OF ARTICULAR CARTILAGE, JOINT MICE AND PATELLAR DISPLACEMENT. GRANVILLE A. BENNETT, WALTER BAUER and STEPHEN J. MADDOCK, Harvard Medical School, Massachusetts General Hospital and Boston City Hospital.

Reparative changes were demonstrable in all but two of seventeen surgically created defects of cartilage. Such repair was manifested in one of three ways: by independent regeneration of original cartilage, by proliferation of connective tissue from the subchondral marrow spaces, or by the ingrowth of pannus from the marginal synovial membrane. A limited ability of cartilage to repair aseptic lesions made entirely within cartilage, by multiplication of original cartilage cells was observed in several of the defects. More active and more nearly complete regeneration of cartilage occurred on the weight-bearing surface of the femoral condyle than on the nonweight-bearing surface of the patellar groove.

In contrast to conclusions of others it was found that neither the presence of surgical defects in cartilage or cartilage and subchondral bone nor the presence of "joint mice," consisting of cartilage or cartilage with attached bone, was a cause of important associated joint changes.

In each joint in which permanent patellar displacement occurred, there were marked intra-articular changes of a type similar to the changes encountered in human hypertrophic arthritis. Such changes became prominent within four weeks and progressed.

THE ANTERIOR LOBE OF THE PITUITARY GLAND AND HYPERTHYROIDISM. LEO LOEB, Washington University.

The effects of administration of extracts of the anterior lobe of the bovine pituitary gland to guinea-pigs are compared with the changes observed in cases of exophthalmic goiter in man.

A RAPID PHYSIOLOGIC TEST FOR THE CORPUS LUTEUM HORMONE. G. W. HART and J. A. MORRELL (introduced by John F. Anderson), New Brunswick, N. J.

A technic is described whereby it becomes possible to complete the physiologic assay of any corpus luteum preparation within five days. The uterus of the rabbit is sensitized by the induction of ovulation as the result of a single intravenous injection of urinary hebin. From twenty to twenty-four hours later, the

animal is castrated, and twenty hours later a subcutaneous injection of the extract to be tested is given and repeated every twelve hours until four injections have been given. Approximately forty-eight hours after the first injection, the rabbit is killed by a blow on the occiput. The uterus is removed and transferred to a tube containing warm oxygenated Locke's solution. When the regular contractions have been fully established, 0.2 unit of extract of the posterior lobe of the pituitary gland in 1 cc. of physiologic solution of sodium chloride is introduced into the Locke solution, and any change in the rate and nature of the contractions is noted. An active extract containing the corpus luteum hormone causes a uterus under these conditions to show either no response to the extract of the posterior lobe of the pituitary gland or some markedly modified response. There is a certain parallelism between the type of response obtained and the degree of proliferation of the uterine mucosa. We have found that when no response to the extract of the posterior lobe of the pituitary gland is obtained, this dosage is equivalent to two Corner rabbit units.

Duodenal Ulcer Following Damage to the Adrenal Glands. Charles McLaughlin (introduced by I. S. Ravdin), University of Pennsylvania.

In a series of dogs, the adrenal glands were damaged by a high frequency coagulating current. The major injury resulted to the cortex, but the medulla was affected. The operation was done in two stages. In fifteen of nineteen animals duodenal and jejunal ulceration occurred. The ulceration was of two types; the one was limited to superficial erosion, while the second was characterized by the heaping margins of the chronic ulcer of man. With the method used, gastric ulceration did not occur.

Some Physiologic Effects of Acetone. M. M. Kunde, University of Chicago.

Acetone in quantities of 2 cc. per kilogram causes an increase in the basal metabolic rate and marked hyperglycemia. Removal of one adrenal gland and denervation of the other prevent the hyperglycemia but do not prevent increase in the basal metabolic rate.

Effects of Total Removal of the Liver in the Monkey (Macacus Rhesus). Stephen Maddock and Andrea Svedberg (by invitation), Boston City Hospital.

The animal was prepared for removal of the liver by preliminary ligation of the portal vein and vena cava as described by Markowitz and Soskin. The results of studies on twenty-five animals are included in the report. Biochemical studies were made using both the Folin-Wu and the Folin method of precipitation. The animals lived for periods varying from twelve to eighteen hours. The results are entirely comparable with the findings previously reported for the dog and the rabbit.

Splenectomy in Dogs with Biliary Fistula; Overproduction of Biliary Pigment. F. B. Queen (by invitation), W. B. Hawkins (by invitation) and G. H. Whipple, University of Rochester.

The output of biliary pigment in a healthy dog with biliary fistula is somewhat constant, but can be modified by certain diets and fluctuates at times owing to unknown factors. A splenectomized dog with biliary fistula may run the usual course of a normal control with biliary fistula for some time, but after a period of weeks or months the splenectomized animal develops cycles of anemia and an extraordinary excretion of biliary pigment. After one or more cycles, the dog dies of anemia or of intoxication. The output of biliary pigment may increase to from five to seven times the normal level. The drop in hemoglobin is entirely

inadequate to explain this great increase in excretion of biliary pigment as due to destruction of hemoglobin and resultant formation of biliary pigment. The hemoglobin does not return to normal levels nor does the biliary pigment fall to the normal base line between these cycles. So far as we know, this is the only condition in which the spleen is essential to life. It indicates that the spleen and the bile together are essential for normal metabolism of pigment. The source of this great excess of biliary pigment is obscure, but the excessive pigment can scarcely be explained as derived only from broken down hemoglobin. This has an important bearing on the understanding of the production of the pyrrole nucleus within the body and its utilization to form either hemoglobin or biliary pigment.

THE EFFECT OF TEMPERATURE ON THE PERMEABILITY OF RESTING AND OF ACTIVATED CELLS TO WATER. MORTON MCCUTCHEON and BALDUIN LUCKÉ, University of Pennsylvania.

It has been shown that the permeability of the living cell to water, like other properties of the cell, varies with temperature. When an isolated cell, such as the spherical egg of the sea urchin (selected because it can be measured accurately), is exposed to hypotonic solutions, water enters the cell more rapidly at higher than at lower temperatures. In the case of the resting (unfertilized) egg, permeability to water, defined as the rate of passage of water per unit area of surface per unit of pressure, has a temperature coefficient approximating a $Q_{10}$ value of 2.7. This value is much higher than would be the case if the passage of water into the cell were purely a process of diffusion. It indicates that with change in temperature there is change in the resistance of the surface of the cell to flow of water. Such a change might be either reversible or irreversible (owing to injury), as previous experiments have shown that injury due to heat is manifested by increased permeability to water. To determine whether the temperature effect is reversible, permeability was determined first at a higher temperature, then at a lower; with other cells the procedure was reversed, measurements being made first at the lower, then at the higher temperature. Permeability was found to be the same at corresponding temperatures, indicating that the effect of temperature is entirely reversible. At the end of each experiment, the eggs were inseminated; subsequently normal cleavage occurred, showing that the cells had not been injured. Activated (fertilized) eggs, which are more permeable to water than are unfertilized eggs, yielded an even higher temperature coefficient, a $Q_{10}$ value of about 3.5.

NORMAL AND PATHOLOGIC PERMEABILITY OF LYMPHATIC CAPILLARIES. STEPHEN S. HUDACK (by invitation) and PHILIP D. MCMASTER, Rockefeller Institute for Medical Research.

Intracutaneous injections in man are predominantly intralymphatic injections, as shown by the use of isotonic solutions of vital dyes. After injection, diffusible vital dyes pass rapidly from the minute lymphatics of the skin to the interstitial tissue. Lymphatic drainage in the normal human being is so rapid as to carry dye from the lower forearm to the axilla in from ten to twelve minutes and render the major lymphatic trunks visible along the route.

When the dye solution is injected at the edge of the ear of the mouse, the lymphatics draining the spot become visible practically at once because of their colored content. The method has made it possible to test the permeability of the wall of the lymphatic capillary. The rapidity with which the dye spreads, secondarily from these vessels to the surrounding tissue varies directly with the diffusibility of the dye, other things being equal. Dyes that fail to pass through the wall of the blood capillary are held back also by the wall of the lymph capillary. Slight causes suffice to produce great alterations in the permeability of the lymphatic vessels. Slight mechanical, thermal or chemical stimulation greatly increases the permeability.

CORRELATION OF MITOCHONDRIAL ALTERATIONS IN RENAL EPITHELIUM WITH SECRETORY ACTIVITY AS DETERMINED BY THE EXTRAVITAL METHOD. JEAN OLIVER, Long Island College of Medicine.

Two recent additions to methods of study of the kidney have made possible a new attack on the problem of the part played by the mitochondria of the renal epithelium in functional activity. These are (1) the demonstration that neutral red is secreted by the tubule cells (Scheminsky, F.: *Arch. f. d. ges. Physiol.* **221**:641, 1929. Oliver, J., and Shevky, E.: *J. Exper. Med.* **50**:15, 1929), and (2) the observation that anatomic processes can be studied extravitally in the perfused organ (Oliver, J., and Smith, P.: *ibid.* **53**:785, 1931).

The kidneys of a single animal, the frog, were compared with respect to the mitochondria. The one kidney was functioning under perfusion in such a manner that the secretory activity, as shown by examination of the urine, was low if not entirely absent, while in the other the epithelial cells were actively secreting the dye, neutral red, in large amounts.

It was found that the anatomic expression of these two different functional states is a replacement of the filamentous mitochondrial structures of the non-secreting epithelium by granulovascular structures in the secreting epithelium. A further study of these granulovacuolar bodies by means of vital, supravital and extravital staining with janus green and neutral red showed that their material, although its fundamental reactions are those of mitochondrial substance, has acquired added characteristics not found in the original mitochondria.

There have been demonstrated, therefore, under rigorously controlled experimental conditions, not only structural alterations in the mitochondria during secretory activity, but also changes of some physical or chemical nature.

Similar relations between secretion and mitochondrial alterations were then demonstrated in the living frog under the physiologic conditions of its natural life.

SULPHYDRYL—ITS EFFECTS ON CELL ORGANIZATION AND DIFFERENTIATION AND THE RELATIONS TO NEOPLASIA. STANLEY P. REIMANN, Lankenau Hospital Research Institute, Philadelphia.

Sulphydryl stimulates cells to divide beyond the normal rate for the species. This higher rate has been correlated directly by Hammett (*Protoplasma* **13**:331, 1931) with the higher differentiation and organization that have been found. Since neoplasias exhibit degrees of differentiation and organization lower than normal for the species, phenomena of cell division alone cannot be responsible for neoplasias. The division must occur in a cell that is constitutionally altered in its organization and differentiation factors. Whether this alteration is in the chromosomes or in the "working" nucleus or in the cell as a whole remains to be discovered. At all events, these experiments show that normal cells stimulated by the naturally occurring stimulus differentiate and organize more; therefore, for less to occur requires that the cells undergoing division be abnormal.

THE ORIGIN OF THE INFILTRATING CELLS IN TRANSMISSIBLE LYMPHATIC LEUKEMIA OF MICE. JAMES S. POTTER (by invitation) and MAURICE N. RICHTER, Carnegie Institution of Washington, Cold Spring Harbor and Columbia University.

Fourteen transmission lines of lymphatic leukemia of mice have arisen in this laboratory by transfer from as many spontaneous cases. Investigations into the nature of the agent have led to a study of the origin of the infiltrating cells in several of the transmission lines.

Since genetic uniformity of the hosts assures 100 per cent susceptibility, and since there are characteristic distribution of lesions and a characteristic interval before death after injection of a given line, it is possible to trace the injected cells

and their descendants in serial sections of tissues taken from animals killed at intervals following inoculation.

The predominating type of cell in the infiltrations of a given line is constant through numerous transfers. The infiltrating cells can be traced to an origin in cells injected into the host. Lesions form and enlarge by infiltration of cells that subsequently divide by mitosis.

During the formation of lesions there is no observable increase in the formation of lymphocytes by the tissues of the host.

The conclusion is reached that the infiltrating cells of a given line of inoculable lymphatic leukemia of mice are descendants of the cells of the original spontaneous case.

THE EFFECT OF MASSIVE EXPERIMENTAL HEMORRHAGES ON THE DOG'S "ERYTHRONE." E. B. KRUMBHAAR and A. R. CAMERO (by invitation), University of Pennsylvania.

The effect of massive hemorrhages was studied with special reference to the size of the red blood cell. Two of the four test animals were bled of 50 per cent of their blood volumes. From a third dog 60 per cent was removed on one day and an additional 30 per cent of the remaining blood on the next. The fourth dog was bled of 50 per cent on one day and of 30 per cent of the remainder on the next. Two intact dogs were used as controls. Direct observations included counts of erythrocytes and reticulocytes, estimations of hemoglobin (Sahli), hematocrit readings, determinations of plasma volume and direct measurement of the diameters of fresh red blood cells with the ocular micrometer. The total number of erythrocytes measured in this way was 13,200. From these direct observations, total cell volume, total blood volume and mean corpuscular volume (Wintrobe) were calculated.

Following the loss of 50 per cent of the blood volume, there was a striking increase in the "scatter" of erythrocyte diameters, with many large cells and almost as many small ones, resulting in only a slight increase in the average diameter. The dogs subjected to maximum hemorrhages (approximately 80 and 90 per cent of the blood volume, respectively) showed a definite increase in average diameter of cells as well as an increase in "scatter." At the time of maximum posthemorrhagic change, the average diameter of the cells was found to be 8.3 microns, with cells ranging from 6.3 to 11.3 microns. The normal average diameter by the method used had been found to be 7.7 microns, with cells ranging from 6.1 to 9.4 microns. In all of the test animals, the calculated mean corpuscular volume reflected somewhat more strikingly the increase in the size of the erythrocyte. The maximum changes were noted between the second and the fourteenth day after the hemorrhages.

There were an expected fall in the erythrocyte count and hemoglobin percentage, a noteworthy reticulocyte rise, a fall in total cell volume, an increase in plasma volume and a more or less constant total blood volume. The blood picture returned to normal after eight weeks.

BONE MARROW IN NEUTROPENIC STATES AND THE PROBLEM OF MYELOID STIMULATION. CHARLES A. DOAN, Ohio State University.

Experimental studies, begun in 1924 and published in 1928, established the direct action of the nucleinate molecule, or of the nucleotides comprising it, on bone marrow in effecting a striking peripheral leukocytosis. More recent studies have shown that daily injections of the nucleotides into the rabbit for a brief period (one week) produces hyperplasia of the myeloid tissues in the marrow, with a gradual increase in the number of granulocytes in the peripheral blood.

The long continued (four months) daily injection of large quantities (1 Gm.) of sodium nucleinate produced a high level of mature granulocytes in the peripheral circulation throughout the experiment, and post mortem, in addition to generalized

hyperplasia of myeloid cells in all bone marrow, ectopic foci of developing myelocytes were found in both kidneys and spleen. The rationale for this action of nucleic acid is in the occurrence of "nonmotile" showers of granular leukocytes under physiologic and most pathologic conditions, with the possibility of the nuclear products thus liberated acting as the normal replacement stimulus in the mechanism of cellular hemostasis.

The results of examination of the blood in two clinical cases of malignant neutropenia in which nucleotide therapy was used will be presented to illustrate the response of the human myeloid mechanism; in the first instance, from a marrow in which foci of myelocytes were still present, even though there were no neutrophilic leukocytes in circulation; in the second, from a marrow hypoplastic or essentially aplastic for myelocytes, but in which their regeneration was stimulated and the subsequent myelocytic maturation followed through careful cytologic studies of the cells appearing in the blood during recovery.

A hypothesis suggesting a factor common to all three procedures—irradiation, blood transfusion and the injection of nucleotide—now advocated in meeting the therapeutic problem of the Schultz syndrome may explain the mechanism by which some clinical recoveries have followed each method of treatment, and may suggest when each in indicated.

SULPHIDE ANEMIA: NONSPECIFIC ACTION OF ANTI-ANEMIC SUBSTANCES. O. M. GRUHZIT, Research Laboratories, Parke, Davis & Company.

The feeding of synthetic monosulphide and disulphide compounds of the general formula R-SH or R-S-S-R to dogs produces in them a severe hemolytic anemia. The anemia is similar to that induced by the feeding of onions and the phenylhydrazine type of compounds. The degree of anemia induced by the sulphides is directly related to the quantity administered. Prolonged feeding may lead to the development of a slight tolerance for the drug, which is readily overcome by an increase in the dosage. Withdrawal of sulphide compounds is followed by recovery to an apparently normal hematic condition. In some animals maintained for over a year on normal propyl disulphide there apparently developed a certain degree of aplasia of the red cell degenerating centers, as the normal level of the blood was not attained inside of several months after withdrawal of the disulphide. A probable aplasia was also noted in one case of human polycythemia vera in which the drug was administered for 109 days until the red cell count was reduced from 10,000,000 to 4,700,000 red cells and hemoglobin from 137 to 100 (Sahli). The patient has not had the drug now for 68 days, and the red cell count and hemoglobin have remained stationary at 4,700,000 and 90 (Sahli).

The ease with which anemia could be induced and maintained by administration of sulphide suggested a use of this type of anemia in the study of anti-anemic substances. On the whole, the early evidence tended to show that substances active against Addison's anemia, such as ventriculin and liver extract, were also active against sulphide anemia. Further studies brought out that this action was nonspecific. Feeding of nonspecific substances, such as iron, ash of liver, lean meat, autoclaved ventriculin or liver extract, at times overcome the sulphide anemia and at other times did not. Injections of crude insulin, with or without liver extract, ameliorated the sulphide anemia. Intravenous and intramuscular administration of potent liver extracts as well as harmless brilliant vital red dye was followed by depression of the hematopoietic system.

CERTAIN QUANTITATIVE ASPECTS OF THE CLOTTING OF THROMBIN. E. D. WARNER (by invitation) and H. P. SMITH, University of Iowa.

The clotting time of thrombin has been used especially as a measure of the concentration of thrombin. To measure thrombin in this way one must be certain that other variables have been eliminated. We have been studying a number of the variables and have been trying, as far as possible, to gain a quanti-

tative concept of the importance of each. Such studies should form a sound basis for further work on clotting.

The present work shows that the clotting time varies markedly with the amount of fibrinogen, as well as with the amount of thrombin.

When we plot clotting time, as ordinate, against the concentration of fibrinogen as abscissa, we obtain a U-shaped curve, with the minimum clotting time occurring when the fibrinogen concentration is optimal. With smaller or with larger amounts of fibrinogen, clotting is delayed. The optical fibrinogen concentration varies somewhat with the amount of thrombin present. To use clotting time as a measure of thrombin concentration, the amount of fibrinogen in the clotting mixture should be controlled.

TWO-COLOR LANTERN SLIDES BY PHOTOMICROGRAPHY. JOHN C. BUGHER (by invitation) and C. V. WELLER, University of Michigan.

A method has been developed in our laboratory for the production of photomicrographs and particularly lantern slides in red and blue without the use of color plates, which have never been fully satisfactory, because of their lack of transparency. By this method, which has been devised by Dr. Bugher, highly transparent lantern slides can be produced in two colors that reproduce satisfactorily the color values of ordinary hemalum and eosin stains.

THE EFFECT OF FASTING OF THE HOST ON CESTODES. DAVID L. BELDING, Boston University.

During its spawning migration in American waters, the adult Atlantic salmon ceases feeding from four to six months. During this period of fasting, certain physiologic changes take place in the salmon, chiefly in the reproductive organs, muscles and digestive tract. At the beginning of the fast, the incidence of tapeworm infection was 40 per cent. After marked atrophy had occurred in the digestive tract, the incidence fell to 9 per cent. During the period of fasting, the salmon had succeeded in ridding themselves of the cestodes, apparently a unique record in the annals of parasitology. (Slides were shown.)

THE PORPHYRIN PIGMENTS OF BACTERIA. CALVIN B. COULTER, Columbia University.

Various procedures of extraction have been carried out in the effort to obtain cytochrome or its derivatives from bacteria. Brewer's yeast, Bacillus phosphorescens and Coryne bacterium diphtheriae have been used. Extraction of yeast and B. phosphorescens with alkali yields a hemochromogen similar to the "cytochrome C" of Keilin. Alkaline extracts of C. diphtheriae differ slightly from this with respect to the position of the main absorption bands. From these extracts as well as from the whole bacteria there have been obtained, by extraction with acetic acid-ether, alpha-hematin and a hemochromogen apparently identical with a porphyrin compound that is found in toxic filtrates of cultures of C. diphtheriae.

This compound has a characteristic absorption spectrum of two bands in the green. It is very labile and breaks down to yield coproporphyrin and the copper compound of coproporphyrin, and may represent a form in which copper is contained within the cell. The amount of this compound has been found to be proportional to the amount of toxin.

QUESTION: Is it then possible to determine the amount of toxin with the spectroscope?

ANSWER: One can estimate the amount of toxin in a culture, even without filtration, by proper spectroscopic examination. With the spectrophotometer we have been able to titrate the toxin. The results are reliable, but do not give as high precision as the titration by inoculation of animals.

SPECIFICITY OF STREPTOCOCCI ISOLATED IN STUDIES OF INFLUENZA. EDWARD C. ROSENOW, Mayo Foundation.

The results of experiments in a restudy of the etiology of influenza will be reported. Evidence of specificity of the streptococcus and other bacteria isolated, aside from the usual cultural reactions, was obtained by inoculating animals in various ways with living cultures and the corresponding filtrates and dead bacteria, and with suspensions and filtrates of nasopharyngeal washings and sputum. The cataphoretic velocities of the streptococcus and other bacteria were also determined, which served as a reliable check in establishing whether cultures were influenzal or not.

The more important symptoms and lesions of influenza, such as prostration, leukopenia, pharyngitis, bronchitis, emphysema and hemorrhagic edema of the lungs, massive hemorrhagic, coalescing bronchopneumonia and empyema, have been reproduced in suitable animals.

THE OCCURRENCE OF BACTEROIDES IN THE FECES. ARNOLD H. EGGERTH and BERNARD GAGNON (by invitation), Long Island College of Medicine.

From 50 to 99 per cent of the organisms grown from normal feces were nonspore-bearing anaerobic bacilli of the genus Bacteroides. The following species, all but two of which are new, have been isolated and studied:

I. GRAM-NEGATIVE BACTEROIDES

A. No gas from peptone
  B. Acid in arabinose and salicin
    C. Acid in mannitol.....B. gulosus
    CC. No acid in mannitol
      D. Acid in rhamnose
        1. Not encapsulated.....B. thetaiotaomicron (Distaso)
        2. Encapsulated.....B. variabilis (Distaso)
      DD. No acid in rhamnose.....B. uniformis
  BB. Acid in arabinose; no acid in salicin
    C. Gelatin liquefied.....B. vulgatus
    CC. Gelatine not liquefied.....B. incommunis
  BBB. Acid in salicin; no acid in arabinose
    C. Acid in xylose.....B. distasonis
    CC. No acid in xylose.....B. uncatus
  BBBB. No acid in arabinose or salicin
    C. Acid in sorbitol.....B. tumidus
    CC. No acid in sorbitol
      D. Acid in rhamnose
        1. Acid in lactose.....B. ovatus
        2. No acid in lactose.....B. vescus
      DD. No acid in rhamnose
        1. Acid in xylose.....B. convexus
        2. No acid in xylose.....B. exiguus

AA. Gas from peptone
  B. Acid in lactose
        1. Acid in arabinose.....B. inaequalis
        2. No acid in arabinose.....B. insolitus
  BB. No acid in lactose; acid in dextrose.....B. varius
  BBB. No acid in dextrose
        1. Milk coagulated.....B. coagulans
        2. Milk not coagulated.....B. siccus

II. GRAM-POSITIVE BACTEROIDES

(Work on this group is incomplete and will be reported at a later time.)

TYPES OF RESPONSE IN LABORATORY ANIMALS TO HUMAN STRAINS OF ASPERGILLUS. GEORGE H. ROBINSON and SAMUEL R. HAYTHORN, Pittsburgh.

Cultures of Aspergillus fumigatus recovered from two infected patients were injected into laboratory animals and the lesions studied. Subcutaneous injection produced abscesses, which later formed pseudotubercles with typical Langhans' giant cells. Intraperitoneal inoculation led to the formation of pseudotubercles, which in some instances broke down and contained central masses that closely resembled actinomycosis. Intratracheal inoculations produced chronic bronchiolitis, pseudotuberculosis and diffuse interstitial pneumonia with lymphoid hyperplasia and formation of germ centers.

Pseudotuberculosis due to aspergilli is well known and is so suggestive of tuberculosis as to make differential diagnosis difficult. The lesions resembling actinomycosis are less well known, but are so similar that special staining is necessary for differentiation.

SOME GENERAL CONSIDERATIONS AND A NEW CLASSIFICATION OF VIRUS DISEASES. EARL B. MCKINLEY, George Washington University.

The virus diseases affect man, animals, insects, fowls, plants and fishes, and are characterized by attributes that set them apart from other diseases such as those that are caused by bacteria and animal parasites. Pathologic, epidemiologic and immunologic differences lend strong support to the belief that filtrable or ultramicroscopic viruses are distinct from bacterial forms, either filtrable or non-filtrable. It is unfortunate that the confusion in regard to filtrable forms of bacteria and true filtrable viruses has been so widely disseminated. While the precise nature of viruses and their relation, if any, to other disease-producing agents are not known, the ultimate solution of the many problems will be best served by the most cautious and conservative interpretation of experimental data. Any classification of the viruses and the diseases that they cause should be based on a careful adherence to what is actually established concerning them. When the subject is systematized, one's comprehension of it becomes more orderly, and when one can separate the material and examine parts of it in an objective manner, one's opinion becomes better crystallized. A new classification of virus diseases is presented, based on the presence or absence of inclusion bodies, on transmissibility and on filtrability of the causative agent. It is expected that as new knowledge accumulates certain changes will of necessity be made, but, in its present form, the classification represents progress and improvement over former attempts to classify a group of agents and diseases in a field involving much debatable terrain.

A RECENTLY DESCRIBED VIRUS DISEASE OF PARROTS AND PARRAKEETS DIFFERING FROM PSITTACOSIS. T. M. RIVERS and F. F. SCHWENTKER (by invitation), Rockefeller Institute for Medical Research.

The widespread outbreak of psittacosis in 1929 and 1930 incited experimental work which quickly resulted in the discovery that the disease is caused by an agent capable of traversing bacteria-tight filters. Thus for the first time a filtrable virus indigenous to parrots was found. Since Amazon parrots were believed to be the chief source of the infection, workers in Brazil sought for evidence of psittacosis in their country. Pacheco, Bier and Meyer encountered a disease in parrots that subsequently was shown to be induced by a filtrable agent. According to their reports, the etiologic agent passes Berkefeld N candles, is not cultivable on ordinary mediums, produces areas of necrosis in the liver and spleen in which are found acidophilic nuclear inclusions similar to those seen in herpes febrilis and virus III infections, and is not pathogenic for pigeons, chickens, mice, guinea-pigs or monkeys. Moreover, these workers stated that the clinical picture observed in infected birds is similar to that of avian psittacosis, and they believe

that the strict adaptation of the virus to the Psittacidae accounts for the absence of human psittacosis in Brazil.

Dr. Pacheco sent us some of his virus in order that its activities might be compared with those of a virus known to have caused psittacosis in human beings. This comparison has been made, and we can confirm the results of the experimental work reported by the Brazilian investigators. We do not agree, however, with the conclusion that the strict adaptation of the virus to parrots and parrakeets accounts for the absence of human psittacosis in Brazil. On the contrary, our experiments with the virus indicate that another filtrable virus producing disease of parrots has been discovered. Its difference from psittacosis is manifested by the fact that the causal agent is nonpathogenic for mammals and produces lesions in avian livers and spleens in which numerous acidophilic nuclear inclusions are found, instead of the "minute bodies" first described by Levinthal as characteristic of psittacosis.

VACCINATION AGAINST YELLOW FEVER WITH VIRUS FIXED FOR MICE AND IMMUNE SERUM, W. A. SAWYER, S. F. KITCHEN (by invitation) and WRAY LLOYD (by invitation), Yellow Fever Laboratory, Rockefeller Foundation.

After preliminary experiments in monkeys, fifteen persons were actively immunized by a single injection of a dried mixture of the living virus of yellow fever, fixed for mice, and human immune serum, with separate injections of enough additional serum to make up the amount required for protection. One person was similarly immunized by injecting immune serum and dried virus separately. By titration of the serums of several of the vaccinated persons in mice, it was shown that the immunity rose in a few weeks to a height comparable to that reached after an attack of yellow fever, and remained there throughout a period of observation lasting six months. Yellow fever virus could not be recovered from the blood of vaccinated persons or monkeys, except when they had received less than the specified amount of immune serum. Neutralization of the virus by immune serum took place very slowly in vitro at room temperature, and could not have been an appreciable factor in the vaccination. It appeared that the immunizing reaction after the vaccination was a part of an infectious process which also caused leukopenia.

THE CELLULAR REACTION IN EXPERIMENTAL TUBERCULOSIS OF THE CORNEA. ESMOND R. LONG and SION W. HOLLEY (by invitation), University of Chicago.

Results previously obtained (Long, Vorwald and Holley: *Am. J. Path.* **7**:555, 1931) indicated that the initial response of the center of the cornea to infection with tubercle bacilli of human type was almost confined to polymorphonuclear leukocytes, which phagocytosed the bacilli and concentrated them in localized lesions. The subsequent development of these lesions varied in different animals, being rapid in the guinea-pig, less rapid in the rabbit and slow in the cat. The leukocytes in the lesions were gradually engulfed and replaced by large mononuclear cells. At the same time, vascularization of the lesion was evident. The fact that large mononuclear phagocytic cells became prominent at the site of infection only after vascularization of the cornea seemed to rule out a local origin for these cells, and indicated that they reached the lesion either through the blood stream or in the walls of the new vessels. It might therefore be expected that an infection of the corneal margin in close proximity to existing blood vessels would attract large mononuclear cells much earlier than an infection more remote. This proved to be the case in an experiment in which, in the same rabbit, two small doses of tubercle bacilli were placed, one in the cornea close to the limbus, and one in the center of the organ. After one day the reaction was almost exclusively polymorphonuclear in both locations; at one and two weeks, when vascularization had not yet reached the center, it was mononuclear at the margin

and polymorphonuclear at the center; at six weeks, when the center was vascularized, the reaction was mononuclear in both places. A double origin for the mononuclear cells taking part in the reaction was indicated by the fact that monocytes and lymphocytes were present in increased number in the vascular lumina, and similar cells were at the same time observed as a thick mantle around the newly developing vessels. The majority of the cells in this mantle appeared to come from the lumen of the vessel, as indicated by migratory figures. But mitotic figures in the adventitia indicated an origin from this source also. Various transitional stages were seen in the cells beyond this mantle, including the final stage, the epithelioid cell.

LOCAL SENSITIZATION OF THE SKIN (ARTHUS' PHENOMENON) PRODUCED IN NORMAL RABBITS AND GUINEA-PIGS BY THE PROTEIN OF TUBERCULIN. FLORENCE B. SEIBERT, University of Chicago.

Contrary to many previous reports, it has been possible to sensitize the normal guinea-pig and the normal rabbit to the protein of tuberculin so that the animal reacts to an intracutaneous injection of the protein exactly as a tuberculous animal or one that has received an injection of dead bacilli reacts. An inflammatory reaction with edema, induration, leukocytic infiltration and necrosis results in both cases.

This sensitization was brought out with less difficulty than that to crystalline egg albumin. It followed treatment with highly purified tuberculin protein, practically free from reducing substances as well as treatment with the less pure fractions.

When a guinea-pig that had been rendered cutaneously sensitive to the tuberculin protein was given a testicular injection of the homologous antigen, the reaction was similar to the testicular reaction of the tuberculous animal to tuberculin, except that it was possibly less intense.

The relative merits of different methods of preparing and purifying the protein in such a way as to preserve its antigenic capacity were studied. When purified merely by ultrafiltration or precipitated by means of ammonium sulphate or trichloro-acetic acid, the protein has excellent antigenic properties for producing cutaneous hypersensitiveness. When heated, as in the preparation of old tuberculin, the protein loses much of its antigenic properties.

THE DIRECT OBSERVATION IN VITRO OF PHAGOCYTOSIS BY MACROPHAGES AND POLYMORPHONUCLEAR LEUKOCYTES. EMILY B. H. MUDD (by invitation) and STUART MUDD, University of Pennsylvania.

Studies conducted for a number of years by Lucké, McCutcheon, Strumia and ourselves have shown that immune serums promote phagocytosis in proportion as they produce certain definite changes in the cohesiveness, wetting properties and iso-electric points of the particles to be phagocytosed. These changes are such as to indicate that the antibodies are modified serum globulins that combine specifically with and form deposits on the surfaces of the antigen, and that the effect of antibodies in promoting phagocytosis is essentially due to their thus forming surfaces on which leukocytes can spread.

The latter conclusion has been corroborated in the present experiments by direct observation and photography of phagocytosis in vitro by both macrophages and polymorphonuclear leukocytes. Phagocytosis by mammalian white blood cells is essentially a process of spreading; the leukocyte surface spreads on the surface of the particle ingested under the action of interfacial tension.

This process of spreading under surface forces is, however, modified by the resistance to deformation of the protoplasm of the phagocytosing cell. The macrophages are, at least under the conditions of our experiments, more resistant to deformation than the polymorphonuclear leukocytes, and the picture of phagocytosis by the two types of cells differs correspondingly.

FURTHER STUDIES ON THE MECHANISM OF FIXATION BY THE INFLAMMATORY REACTION. VALY MENKIN (introduced by S. Burt Wolbach), Harvard Medical School.

I have recently shown that various foreign substances or bacteria injected into an area of inflammation are fixed *in situ* and fail to drain readily into the tributary lymphatic vessels, while their intravenous injection results in rapid accumulation in the inflamed area. This accumulation is partly the result of the increased permeability of the capillaries, but is also the result of the inability of these substances to escape from the site of inflammation. The retention or fixation of these substances at the site of inflammation has been shown to be due to mechanical obstruction in the form of thrombosed lymphatic vessels and a fibrinous network in tissues distended with edema. In addition to these histologic findings, a second line of evidence to support the hypothesis that mechanical obstruction is the explanation of fixation has been presented by the failure of either dye or bacteria to penetrate the inflamed area when injected at its periphery.

Present studies are concerned with a third group of experiments corroborating further this hypothesis. On the basis of the in vitro observation of Foulger and Mills that urea in high concentrations delays or inhibits clotting of blood by "peptizing" fibrin, I have studied the effects of concentrated urea solutions on the fixation of foreign materials at the site of inflammation with the following results:

1. When injected simultaneously with the inflammatory irritant (aleuronat), urea (50 per cent or, in some cases, 30 per cent) inhibits either wholly or in part the fixation of graphite and of iron in the inflamed peritoneal cavity, allowing free or partial dissemination of these foreign substances to the retrosternal lymph nodes. When the injection of urea follows the onset of inflammation produced by aleuronat in the peritoneal cavity, inhibition of fixation of graphite also occurs. The intensity of this inhibition seems to vary in inverse relation to the length of time elapsing between the injection of aleuronat and that of urea.

2. These results have been correlated with histologic findings, inhibition of fixation being associated with the absence of thrombosis in lymphatic vessels. Likewise in some of the experiments in which the addition of concentrated urea to the inflammatory irritant produced only partial fixation of graphite particles, histologic studies revealed small thrombi occluding in part the lumina of the retrosternal lymphatic vessels.

3. When injected into a normal peritoneal cavity, concentrated urea by itself sets up an inflammatory reaction. However, fixation of graphite does not occur. That concentrated urea (20 to 50 per cent) alone causes increased permeability of capillaries is shown by the accumulation of trypan blue from the blood stream in cutaneous areas almost immediately after these areas are subjected to injection of urea. Histologic sections of skin some hours after injection of urea reveal the usual leukocytic reaction accompanied by considerable extravasation of red cells.

4. Penetration of trypan blue when injected into an area of skin at its periphery takes place when the area has previously been subjected either to injection of urea followed by a suspension of cultures of Staphylococcus aureus, or to injection of urea alone.

5. Studies in vitro show that when inflammatory exudate is added to 50 per cent urea solution, clotting of the exudate is prevented. Addition of concentrated urea solution to coagulated exudate dissolves the coagulum either completely or partially. This solvent action is facilitated if the urea is added very soon after clotting occurs.

These experiments demonstrating the inhibitory effect of concentrated urea on fixation of foreign substances at the site of inflammation, correlated with the histologic findings and with the fact that concentrated urea has been shown to possess a solvent action on fibrin, furnish the third line of evidence as to the rôle of thrombosis of lymphatic vessels and of deposits of fibrin in explaining fixation at the site of inflammation.

LOCAL FORMATION OF ANTIBODIES BY THE NASAL MUCOSA. T. E. WALSH (by invitation), F. L. SULLIVAN (by invitation) and PAUL R. CANNON, University of Chicago.

Previous work by us has shown that injection of antigen into an area of skin in which macrophages have been mobilized may lead to local formation of antibodies. Similar experiments have been performed on the nasal mucous membranes of rabbits, with similar results. Daily instillations or insufflations of a formaldehydized vaccine of Bacterium paratyphosum B at daily intervals for at least ten days have led to local formation of specific agglutinins. These have been demonstrated by the simultaneous titration of glycerol-salt solution extracts of these tissues, liver, spleen, blood serum and kidney against a suspension of living cultures of B. paratyphosum B. Instillations for less than this period have given inconclusive or negative results. Extracts of the nasal mucosa of normal rabbits contained no agglutinins for B. paratyphosum B at a dilution of 1:120 or above. Extracts of nasal mucosa of rabbits immunized subcutaneously showed no agglutinins at a dilution of 1:120, although the titers of spleen, liver and blood serum ranged from 120 to 1,920. The irritation of the nasal mucosa of subcutaneously immunized rabbits by instillations of 1 part of solution of formaldehyde, U. S. P., to 300 parts of physiologic solution of sodium chloride ("normal saline") did not lead to a mobilization or concentration of agglutinins in the nasal mucosa.

We conclude, therefore, that specific agglutinins may be formed locally by adequately repeated application locally of the appropriate antigen.

THE PROTECTIVE ACTION OF ANTIBODY IN IMMUNIZED ANIMALS DEPRIVED OF LEUKOCYTES. ARNOLD R. RICH and CLARA M. MCKEE (by invitation), Johns Hopkins University.

Immunized animals were treated with benzene to remove their leukocytes, and were then inoculated intracutaneously with virulent pneumococci. In the immune, leukocyte-free body, the presence of antibody influences profoundly the character of the growth of the bacteria and the course of the infection. The bacteria as they proliferate adhere to themselves and to the tissues and are thus held fixed at the site of inoculation for hours after controls have died with septicemia. This fixation occurs and can be maintained for forty-eight hours or more in the complete absence of local inflammatory exudate of any sort. It is, therefore, the antibody content of the body fluids, not inflammation, that is responsible for the prevention of immediate spread of pneumococci in the immune body. However, in the absence of leukocytes the local growth of the immobilized bacteria proceeds uninterruptedly, and the animals eventually succumb even when their plasma is potent in passively protecting nonimmune, normal animals. The humoral antibody, therefore, performs the important protective function of preventing the immediate spread of the bacteria throughout the body, but acquired immunity creates no condition of the fluids or of the fixed tissues that can prevent the progressive growth of the bacteria in the absence of the leukocytes.

INFLUENCE OF CONCENTRATION OF SOME ORGANIC SOLVENTS ON PRECIPITATION AND DENATURIZATION OF SERUM PROTEINS AND ANTIBODIES. M. H. MERRILL (by invitation) and M. S. FLEISHER, St. Louis University.

Serum proteins can be completely precipitated at room temperature (22 C.) by concentrations of alcohol or of acetone above 90 per cent. Such precipitates are completely soluble in isotonic salt solution or in distilled water. Various factors, such as hydrogen ion concentration, time and presence of electrolytes, must be considered.

Immune serums thus precipitated by alcohol or by acetone can be dried by further extraction with ether without loss in solubility or in activity.

BASIC PRINCIPLES OF PATHOLOGIC REACTION IN THE BRAIN. WILDER PENFIELD (introduced by I. S. Ravdin), McGill University, Montreal.

The work of many investigators has served to simplify certain aspects of neuropathology. Neuroglia and microglia are delicate indicators of the functional condition of the brain. The chief pathologic forms of these cells are outlined in the hope that pathologists may utilize more widely the basic principles underlying these changes as a guide to an understanding of the condition of the brain even when the primary pathologic process may be situated elsewhere.

These principles may be used as a guide without allowing recent confusing contributions to cloud the picture until time has been allowed for substantiation or disproof.

THE ISOLATION OF THE ORGANISM OF BARTONELLA MURIS ANEMIA. DAVID PERLA and J. MARMORSTON-GOTTESMAN (introduced by David Marine), Montefiore Hospital.

An organism has been isolated from the blood of splenectomized anemic albino rats which we believe to be the etiologic agent of Bartonella muris anemia. The organism is obtained in pure culture on Noguchi's leptospira medium at room temperature after an incubation period of twelve days. It is gram-negative, actively motile on solid and semisolid mediums and measures from 0.4 to 3.2 microns in length and from 0.2 to 0.4 micron in width. In the initial culture it grows very slowly. After repeated subcultures and passages through animals it grows on the usual enriched culture mediums without blood within forty-eight hours. Neither acid nor gas is formed on twelve of the ordinary sugars. On solid mediums, it forms glistening pinpoint colonies that soon coalesce and form a tenacious growth over the surface. Blood cells in culture mediums are not hemolyzed. Cultures on solid mediums have a characteristic sweet pineapple odor.

The organism is nonpathogenic for adult rats of carrier stock, adult rabbits and adult guinea-pigs. A severe anemia was produced in fourteen 3 week old rats, three 3 week old guinea-pigs and three 3 week old rabbits by intraperitoneal injections of 0.5 cc. of the culture from leptospira medium. The organism was reisolated during the course of the anemia from the blood, liver and spleen. Occasionally bartonella bodies were found in the red cells. The blood of these animals was infectious for animals of the same age. After repeated passages through animals, the organism showed enhanced virulence and a moderate anemia was produced in Wistar splenectomized adult rats of noncarrier stock. There is a striking similarity of Bartonella muris to Bartonella bacilliformis of Oroya fever culturally as well as morphologically, and the identity of the two organisms is suggested.

A TUMOR-LIKE CONDITION IN RABBITS INDUCED BY A FILTRABLE AGENT. RICHARD E. SHOPE (introduced by Carl Tenbroeck), Rockefeller Institute for Medical Research, Princeton, N. J.

From subcutaneous tumors of a wild cottontail rabbit has been secured an agent that, when injected subcutaneously or intratesticularly into the domestic or the wild rabbit, produces at the site of inoculation a large, firm, tumor-like mass composed of rapidly growing connective tissue cells. This mass reaches its maximum size in from ten to twenty days in the domestic rabbit and then slowly regresses. It persists much longer in the wild rabbit. No metastases have been detected. The disease is never fatal, and there are no systemic symptoms. It is transmissible in series. One infection renders a rabbit immune, and serum from such an immune animal neutralizes the etiologic agent. The agent passes Berkefeld V and N filters and resists glycerination at the temperature of the refrigerator for at least eighty-six days. It is not demonstrable in the blood stream. Intravenous and intraperitoneal injection of the agent into rabbits is without effect. White rats and mice, guinea-pigs and chickens are not susceptible to infection

with it. Sections of the skin overlying the tumors in the original animal showed lesions of the epidermis strikingly like those of Molluscum contagiosum. Similar lesions have not been observed in inoculated animals. This tumor-like disease bears a peculiar relationship to infectious myxoma. Although the clinical and pathologic pictures are very different, and although serum from a rabbit in which the tumor has regressed fails to neutralize the virus of infectious myxoma, a rabbit convalescent from the tumor-like disease is resistant to infection with the virus of infectious myxoma.

THE CIRCULATION OF THE LIVER IN RELATION TO RESTORATION FOLLOWING PARTIAL REMOVAL. FRANK C. MANN, Mayo Foundation.

One of the most outstanding characteristics of the liver is its ability to undergo restoration after injury or partial removal. A physiologic need for hepatic tissue has usually been the factor to which is ascribed the quick and complete restoration of the liver after partial removal. The results of various investigations by my associates and myself indicate that the major factor causing restoration of the liver after partial removal is the portal circulation. This statement is based on the following facts: (1) restoration in the rat is decreased following partial occlusion of the portal vein; (2) restoration usually does not occur in a dog with Eck fistula; (3) restoration usually does not occur in the chicken, in which species there is a natural anastomosis between the portal and the systemic venous system; however, if the flow of blood through the liver of the chicken is increased by occlusion of the postcava, restoration occurs to a marked degree; (4) restoration does not occur in a dog in which a stoma between the vena cava and the portal vein is made without ligation of either vessel.

These results indicate that restoration of the liver after partial removal is owing to the need of restoring the portal pathways. The relationship of these observations to pathologic conditions of the liver is considered.

THE MEGALOBLAST AS A NORMAL STAGE IN THE DEVELOPMENT OF THE ERYTHROCYTE. RAPHAEL ISAACS, Simpson Memorial Institute for Medical Research, Ann Arbor, Mich.

Many hematologists, including Naegeli and Piney, following Ehrlich, consider the megaloblast as entirely separate from the precursors of the normal red blood cell, absent from normal adult bone marrow, present in the fetus, and reappearing in pernicious anemia. Recent studies of films made from serum suspensions of bone marrow showed that the megaloblast (with reticular chromatin pattern) was present in the sternal bone marrow of more than fifty consecutive patients suffering from many different diseases. In a specimen of normal marrow, the number was 38,700 per cubic millimeter. In pernicious anemia there is a marked diminution in number as long as adequate liver or ventriculin therapy is given, but the number increases during the relapse. With the use of this therapy, there is first an increase in the number of megaloblasts in the peripheral circulation followed by an increase in the number of normoblasts, then in that of the reticulocytes and finally in that of the adult erythrocytes. In films made from serum suspensions of bone marrow, all types of transitional stages between the megaloblastic and the normoblastic cell can be demonstrated.

EXPERIMENTAL MASSIVE ATELECTASIS BY BRONCHIAL STENOSIS AND ITS EFFECT ON PULMONARY TUBERCULOSIS IN DOGS. ARTHUR J. VORWALD and WILLIAM E. ADAMS (introduced by Esmond R. Long), University of Chicago.

Since one of us (Adams) in 1930 produced massive atelectasis of lung tissue by bronchial stenosis in dogs, this form of treatment was undertaken in cases of pulmonary tuberculosis produced experimentally in dogs.

Massive atelectasis of two or more lobes was produced from two to six weeks subsequent to infection, by cauterizing the mucosa of the corresponding bronchi

with silver nitrate. Most of the animals died or were put to death by the end of four months. The period of infection and the degree of stenosis and subsequent atelectasis of the lung determined the amount of tuberculous tissue that developed. In those lobes in which incomplete stenosis of the bronchial lumen without collapse resulted, there was less tuberculous involvement than in other inflated lobes. In a few animals atelectasis was not attained, either because the animal died before the time required for complete stenosis of the bronchus, or because of physiologic anastomosis between the lobe in which the stem bronchus was stenosed and the normally inflated lobes. In the majority of animals, however, the desired massive atelectasis was obtained. The lobes so collapsed revealed either total absence or decided decrease both in the number of stainable tubercle bacilli and in the tissue reaction to them, whereas the control inflated lobes, in the same animal, contained many tubercles varying in diameter from 1 mm. to 1 cm. In many cases, the inflated lobes contained tubercles with massive caseation and fairly extensive cavitation. Tubercle bacilli in these inflated lobes were demonstrable in countless numbers, particularly in those animals in which the reaction had resulted in caseation and cavitation.

In general, the macroscopic and microscopic observations at autopsy indicate that this method of bronchial stenosis accompanied by permanent massive atelectasis is of unmistakable value in the treatment of experimental pulmonary tuberculosis, when the tuberculous process is concentrated in one or two lobes.

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## CHICAGO PATHOLOGICAL SOCIETY

*Regular Monthly Meeting, May 9, 1932*

R. H. JAFFÉ, *President, in the Chair*

THREE DIFFERENT TYPES OF TUMORS ARISING FROM THE INFUNDIBULAR RESTS OF THE CRANIOPHARYNGEAL DUCT. H. A. MCKINLEY and ARTHUR WEIL.

At the anterior surface of the infundibulum, islands of squamous epithelium are found, an upper and a lower group, which are separated by the pars tuberalis. The latter has been described by Tilney in animals and by Atwell in human embryos as a sheathlike layer of glandular epithelium. Both types are considered rests of the craniopharyngeal duct. Tumors arising from these groups of cells are adamantinomas, simple squamous epithelial papillary cysts (Duffy) and more complicated teratomas.

Most tumors of the first group seem to be malignant in that they infiltrate the surrounding brain tissue. Most of the squamous epithelial papillary cysts are benign and indent the floor of the third ventricle. An example of each type is described:

1. An adamantinoma in a boy, aged 8 years and 10 months, produced the first symptoms of impairment of vision seven years before death. The tumor had the typical arborization of epithelial cells with an outer layer of ameloblast-like cells and an inner stellate reticulum. It was embedded in a loose stroma of argyrophil connective tissue. Breaking through the floor of the third ventricle, it invaded the walls of this structure and occluded the foramina of Monro. A marked hydrocephalus of the lateral ventricles resulted.

2. A squamous epithelial papillary cyst in a man 32 years old began with impaired vision six months before examination (operated on by Dr. L. Davis). It was cystic and was separated by the thickened pia-arachnoid from the floor of the third ventricle. It consisted of layers of squamous epithelium bordered by cuboidal cells at the outer surface that formed islands of degenerated cells, which were replaced by collagenous connective tissue. Around these islands were palisades of more cylindric cells. No stroma was present.

3. The third tumor was a benign suprasellar growth, which consisted of squamous epithelium and glandular tubules. At the free surface, vacuolated glandular epithelium was found. A loose stroma surrounded the cellular masses. Within the tumor were foci of capillaries and fibroblasts, surrounded by one layer of cuboidal epithelium. This tumor may represent a derivative of the pars tuberalis, because it contained glandular elements together with squamous epithelium similar to the structures described by Tilney and Atwell.

LYMPHOGRANULOMA INGUINALE. I. PILOT and L. AMTMAN.

Lymphogranuloma inguinale has been reported as climatic or tropical bubo. The disease is prevalent in Europe and in the United States. By means of a specific skin test (Frei test) many cases previously called inguinal adenitis of possible tuberculous, syphilitic or chancroid origin are now grouped under this clinical entity. Cases have been reported from the United States, but the diagnosis was largely based on the clinical symptoms and microscopic sections. Our three cases, all occurring in men, are the first to be reported from Chicago in which the diagnosis was verified by cutaneous reactions with diagnostic material sent by Frei. This material is the heated exudate aspirated from the glands.

Apparently venereal, the etiology is obscure. Investigations point to a filtrable agent or virus that localizes in the regional lymph glands. Transmission is best obtained in monkeys by intracerebral injection or more recently by inoculation in the prepuce. We were unable to obtain transmission with the pus of two patients, which was inoculated subcutaneously into guinea-pigs.

The inguinal glands enlarge, the capsule thickens, and often the glands become fixed owing to peri-adenitis. Liquefaction occurs, and a thin purulent material may rupture through the skin, with resultant multiple fistulas.

Microscopically, the appearance is not absolutely characteristic. There is diffuse hyperplasia with a distinct tendency to fibrosis. Many plasma cells appear. The softened regions usually contain many polymorphonuclear leukocytes. Giant cells are present occasionally. Smears, stains, cultures and guinea-pig inoculation reveal no tubercle bacilli.

The first patient had been in Nicaragua for several months and noted the adenitis five weeks after returning to the United States. With the enlarging glands, chills and fever developed. The condition was bilateral, and on the left side the glands became adherent to the overlying skin. Thin pus was aspirated, which yielded only Staphylococcus albus. A gland was removed, which on section appeared grayish red and revealed small foci of suppuration from 2 to 5 mm. in diameter. Microscopically, the appearance was that of chronic lymphadenitis and peri-adenitis with multiple foci of liquefaction necrosis.

The second patient had not been out of Chicago for two years. A mass was noted as slowly developing in the left groin. A gland was removed, which was soft and grayish red and contained small abscesses. Microscopically, numerous plasma cells and occasional giant cells were observed. Smears and cultures did not reveal organisms. The Frei antigen gave a strong positive cutaneous reaction in both of these patients.

The third patient had been in Chicago for five years. He had enlarged glands and numerous fistulas discharging a thin, gray, sterile exudate. Antigens prepared for the second patient from his own gland, as well as one prepared by Frei in one of his cases, gave positive reactions.

DISCUSSION

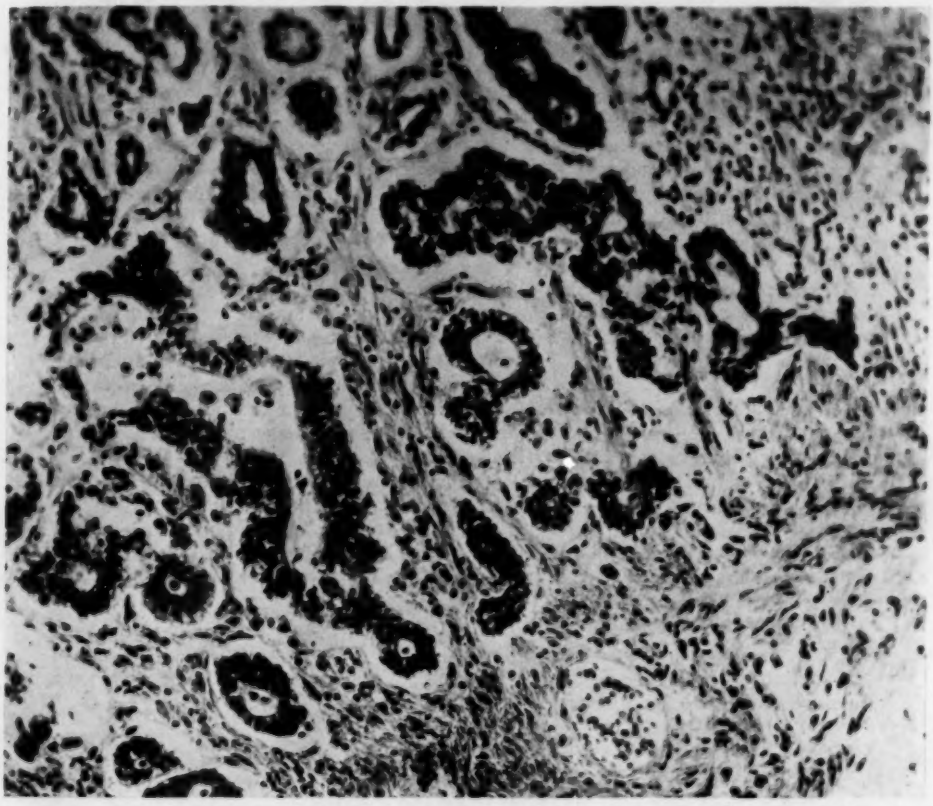
M. FERNAN-NUNEZ: I saw two patients in Nashville, Tenn., who were clinically identical with others seen in the tropics and subtropical regions where this disease is prevalent.

G. W. SCHELM: A patient in North Chicago had similar lesions with ulcerations of the thighs.

R. H. JAFFÉ: The term used for this disease is unsuitable, and some other more appropriate name should be found.

CARCINOMA OF THE STOMACH IN A CHILD AGED THREE YEARS. CORNELIUS S. HAGERTY and STANLEY GIBSON.

Carcinoma of the stomach occurs so rarely in children that there are only six published records of its occurrence in persons aged less than 10 years. Some doubt exists in regard to two of these descriptions because of the uncertainty that the carcinoma was primary or secondary in the stomach. Widerhofer (*Jahrb. f. Kinderh.* **2**:194, 1859) recorded multiple nodules of carcinoma in the gastric mucosa, intestines, gallbladder, urinary bladder and pericardium of an infant aged 15 days. He did not describe the origin of the primary tumor.



Photomicrograph illustrating the carcinoma tissues in the wall of the stomach.

Kaulich (Osler, W., and McCrae, Thomas: Cancer of the Stomach, Philadelphia, P. Blakiston's Son & Co., 1900, p. 16) in 1864 described a carcinoma of the stomach in a child aged 1½ years. Cullingsworth (*Brit. M. J.* **2**:255, 1877) reported an ulcerated cylindric cell carcinoma of the pylorus of the stomach of an infant. Kuhn (cited by Williams, W. R.: *Lancet* **1**:1259, 1897) in 1866 recorded a probably congenital adenocarcinoma of the stomach. Ashby and Wright (The Diseases of Children, ed. 4, New York, Longmans, Green & Co., 1900, p. 113) described pea-sized nodules of carcinoma in the stomach and duodenum of a child aged 8 years. Karl (*Deutsche med. Wchnschr.* **41**:373, 1915) reported a tumor excised from the stomach of a child aged 9 years, which histologically was a primary carcinoma.

The clinical diagnosis of carcinoma of the stomach in infants and young children is difficult because the disease is unusual at this age of life and is rapidly fatal. The prominent symptoms are loss of appetite, anemia, vomiting, eructations and enlarged abdomen. Pain is rare, and emaciation is usually absent because of the rapid growth of the tumor.

A white girl, aged 3, entered the pediatric service at St. Luke's Hospital, Chicago, Jan. 26, 1932, because of loss of appetite and anemia for three months and an appreciable enlargement of the abdomen for four days. There was a large, nodular, tender mass in the right side of the abdomen, and the feces contained occult blood. The erythrocyte count was 1,110,000; the leukocyte count, 21,350; the hemoglobin was 12 per cent. An exploratory operation January 30 by Dr. S. W. McArthur disclosed metastatic tumor nodules in the liver. The primary tumor was not found. Death occurred on Feb. 2, 1932.

The essential results of the autopsy (Graham A. Kernwein) were: primary ulcerated carcinoma of the cardia of the stomach (perforated); multiple metastases to the liver; marked anemia; acute general fibrinous peritonitis.

The abdomen was markedly distended and contained 270 Gm. of a green-yellow serofibrinous exudate. With the stomach opened along the greater curvature, the lining of the cardia was found replaced by an annular, ulcerated tumor 12 cm. long and 6 cm. wide. The upper level of the ulcer reached the esophagus, and it extended on both the anterior and posterior walls for 6 cm. The base of the ulcer was firm, granular, friable and irregularly pitted. There was a small crescentic perforation of the gastric wall 4 cm. from the upper edge of the ulcer and near the lesser curvature. The edges of the growth were firm, undermined and raised, and averaged 1.2 cm. in width. The surface of the elevated edge was continuous with the pale, gray, edematous mucosa of the stomach. The liver weighed 800 Gm. Under the capsule were many protruding nodules of tumor tissue, and practically two thirds of both lobes consisted of circumscribed nodules of soft, friable, yellow-gray tissue mottled with hemorrhages. The liver tissue otherwise had marked cloudy swelling and fatty changes.

Sections of the tissues from the margin of the gastric tumor showed that the mucosa ended abruptly at the margin of the ulcerated growth and the overhanging ledge. The submucosa and muscularis were invaded by cords and masses of epithelium, differentiated slightly into glandular structures. An abundant connective tissue stroma supported these cells. The metastases in the liver had essentially the same structures.

*Summary.*—There seem to be only six recorded accounts of primary carcinoma of the stomach in children aged 10 or less. A glandular carcinoma of the cardia of the stomach in a child aged 3 is reported. Vague symptoms of the carcinoma appeared from three to four months before death.

DISCUSSION

R. H. JAFFÉ: Teratomas may arise in the stomach. I wonder if this began as such a growth and with proliferation of the epithelium.

PONTILE HEMORRHAGE IN YOUTH. E. C. PIETTE and E. F. TRAUT.

A woman, aged 25, with nephritis and hypertension for two years, poor vision and headaches, suddenly became unconscious. The systolic blood pressure was 200 mm. of mercury; the diastolic, 100. The urine contained large quantities of albumin and many casts. The spinal fluid was dark red with blood. Death occurred four hours after the onset of coma.

A pontile hemorrhage 4 by 4 by 3 cm. had destroyed almost the entire brain substance below the aqueductus from the mammillary body to the medulla. The floor of the fourth ventricle was lifted up by the hemorrhage, and its cavity was obliterated. The hemorrhage extended laterally into the brachia. Therefore practically all the nuclei of the fifth, sixth, seventh and eighth nerves and the frontal parts of the vagus, accessorius and hypoglossus were more or less completely

destroyed. The hemorrhagic area was dry and crumbling; its outlines were irregular and did not correspond to the distribution of an artery. One branch of one of the arteria medianae pontis located in the center of the hemorrhage appeared torn and possibly represented the point from which the hemorrhage originated.

The kidneys were small, each weighing about 100 Gm. Their capsules were adherent. The cortices were narrow. The heart had marked concentric hypertrophy. It weighed about 350 Gm.

Microscopic examination of various cerebral vessels of larger caliber showed only moderate sclerotic changes, evidenced by thickening of the elastica interna. Detailed examination of various parts of the brain substance near and within the hemorrhagic area showed that a few isolated arterioles were markedly narrowed. Their walls were hyalinized.

Microscopically, the kidneys showed advanced subacute and chronic changes. There were some foci of lymphocytic and plasma cell infiltration, increase in fibrous tissue and calcification of tubular epithelium. The arterioles had few if any sclerotic changes.

DISCUSSION

R. H. JAFFÉ: Probably this hemorrhage had a uremic basis.

# Book Reviews

**Roentgenologic Studies of Egyptian and Peruvian Mummies.** By Roy L. Moodie, Paleopathologist to the Wellcome Historical Museum, London. Berthold Laufer, Curator of Anthropology, Editor. Anthropology Memoirs, Field Museum of Natural History Founded by Marshall Field, 1893. Volume 3. Paper. Price, $5. Pp. 66, with 76 plates. Chicago: Field Museum of Natural History, 1931.

In 1926, the Field Museum installed an x-ray equipment for the study of specimens in its collection. It was one of the leaders among museums of natural history, if not the first, to make systematic use of this method of research. Some of the results are shown in the present volume. It is superbly illustrated with photogravure reproductions of the admirable roentgenograms made by Miss Anna R. Bolan, of the Field Museum staff. The contents of mummy wrappings and cases are revealed in a striking and dramatic fashion. The roentgenograms showing the skeletons of a little boy and his sister side by side, bodies embalmed and wrapped from which parts are missing, which probably were lost by the embalmers, and the supposed mummy of a cat, all of which was faked except the cranium, must interest any observer. Some specimens are illustrated by photographs. The text by Roy L. Moodie discusses the processes of mummification and the diseases of ancient Egypt and Peru. Among the pathologic conditions described are arthritis deformans, pyorrhea alveolaris, dental caries, impacted teeth, injuries of the skull, trephining of Peruvian skulls and symmetrical osteoporosis. Interesting are the roentgenogram of an Egyptian mummy with a tortuous calcified artery, a probable hydrocephalus in a Peruvian child, a roentgenogram of a Peruvian skull with a tumor, apparently osteosarcoma, and photographs of Peruvian skulls with osteomas of the external auditory meatus. A case of symmetrical osteoporosis of the frontal bone of a child in which trephining had been done is important, as it indicates that the disease of the bone may have been the motive for the operation. The reason for the operation is not apparent in most cases of prehistoric trephining.

**Neoplasms of Domesticated Animals.** By William H. Feldman, D.V.M., M.D., Division of Experimental Surgery and Pathology, the Mayo Foundation, Rochester, Minn. With a Foreword by Charles H. Mayo, M.D. Cloth. Price, $6 net. Pp. 410, with 193 illustrations. Philadelphia: W. B. Saunders Company, 1932.

The prominence of experimental work with cancer in animals during the past thirty years has given the tumors of animals a large importance in the study of malignant disease. Previously there has been available no book systematically discussing the tumors of lower animals, a want now partly met by Feldman's contribution. Primarily written to supply the needs of students and practitioners of veterinary medicine, the book deals chiefly with tumors in the animals handled by the veterinarian, and discusses them largely from the standpoint of the general pathology of the new growths, with numerous excellent illustrations that demonstrate the identity of the neoplasms of animals with those seen in man. The work seems well adapted for use by the veterinarian, as intended. It will also be of use to the general pathologist, who often meets with tumors in animals from one source or another. The investigator of the problem of tumors will find the bibliography useful, and it will often serve as a source of useful information concerning comparative pathology, although it is by no means a complete guide to the widely scattered literature of this field. It serves to emphasize the serious failure of the Bureau of Animal Industry in neglecting to have recorded in avail-

able and adequate manner the innumerable observations of its inspectors on the tumors found in the abbatoirs of the United States. Here is a vast and invaluable material that has been wasted.

**Histopathology of the Central Nervous System. An Introduction by Means of Typical Microphotographs and a Short Text.** By Prof. Dr. L. Bouman, Utrecht, and Prof. Dr. S. T. Bok, Leiden. Price, 25 florins. Pp. 37, with 212 figures on 53 plates. Utrecht: A. Oosthoek's Publishing Company, 1932.

The book is an atlas of 212 excellent photographs printed on glossy, photographic paper and accompanied by a text of 37 pages. The photographs, or rather photomicrographs, are for the most part splendidly done and, though not in colors, convey an excellent idea of the subjects treated. It is not a systematic or detailed book on neuropathology, but a photographic illustration of the most important phases of normal and pathologic histology of the central nervous system. The peripheral nerves, malformations of the nervous system and tumors were not included. Syringomyelia was excluded from the review, as the authors consider it a tumor formation. The Spanish staining methods and classification of the glia elements have been given careful consideration, but microglia is classified by them not as connective, but as neuroglia, tissue. Because of the remarkably clear and concise manner with which the fundamental topics of neuropathology have been dealt, the book will prove extremely valuable and useful to the busy general pathologist and to the clinician.

**Medical Aspects of Old Age: Being a Revised and Enlarged Edition of the Linacre Lecture, 1922.** By Sir Humphry Rolleston, Bart., G.C.V.O., K.C.B., M.D., Regius Professor of Physic in the University of Cambridge. Second edition. Cloth. Price, $3. Pp. 205, with 7 portraits. New York: The Macmillan Company, 1932.

There are ten chapters in the book: duration of life, onset of old age, factors influencing longevity, causes of old age, normal structural changes in old age, the description of old age in the twelfth chapter of Ecclesiastes, distinction between healthy and morbid old age, diseases of old age, old age and carcinoma. There are an index of persons and one of subjects. The seven illustrations show persons reputed to have lived from one hundred to one hundred and eighty-five years. The style is clear and pleasing with occasional touches of gentle humor. An air of quiet and thoughtful consideration prevails. Except for incidental references, medical treatment in old age has not been considered.

**Tuberkulose als Schicksal. Eine Sammlung pathographischer Skizzen von Calvin bis Klabund 1509-1928.** Von Dr. Erich Ebstein. Mit einer Einführung von Prof. Dr. Georg B. Gruber. Pp. 191, with 8 illustrations. Price, 6.50 marks. Stuttgart: Ferdinand Enke, 1932.

This book was published after the death of the author. It contains about fifty short pathographic sketches of remarkable persons who lived in the period from 1509 to 1928. The purpose of these sketches was to furnish a basis for a closer study of the mind in pulmonary tuberculosis, especially of gifted persons, but this study was not completed when the author died, and in its place is an introductory chapter on the psychology of tuberculosis by Georg B. Gruber. The book contains many interesting data and references. It will be of special interest to students of tuberculosis and of biography.

# Books Received

ABHANDLUNGEN AUF DEM GEBIETE DER ALLGEMEINEN PATHOLOGIE UND PATHOLOGISCHEN ANATOMIE. Zweiter Band. Mitteilungen des Pathologischen und Histologischen Institutes der KGL. Ung. Franz Josef Universität, Szeged, Ungarn. Herausgegeben von Dr. Josef Balo, O. O. Universitätsprofessor Direktor des Institutes. Szeged: 1931.

UEBER WACHSTUM UND RÜCKGANG; UEBER STANDARDISIERUNG, INDIVIDUALISIERUNG UND BAULICHE INDIVIDUALTYPEN IM LAUFE DES NORMALEN POSTFÖTALLEBENS, KONSTITUTIONSANATOMISCHE STUDIEN AN KANINCHEN. Von J. Aug. Hammar, Professor Emer. an der Universität Uppsala. Pp. 540, mit 132 Tabellen, 48 Text Abbildungen und 10 Abbildungen auf Tafel I-V. Leipzig: Akademische Verlagsgesellschaft M.B.H., 1932.

REPORT OF THE HAFFKINE INSTITUTE FOR THE YEAR 1930. By Major L. A. P. Anderson, I.M.S. Offg. Director Haffkine Institute. Price, 8 pence 6 annas. Pp. 76. Bombay: Government Central Press, 1932.

SPECIAL CYTOLOGY: THE FORMS AND FUNCTIONS OF THE CELL IN HEALTH AND DISEASE. A Textbook for Students of Biology and Medicine. Edited by Edmund V. Cowdry, Washington University, St. Louis, Mo. Edition 2. Three Volumes. Price, $30. Pp. 1,838, with 757 illustrations. New York: Paul B. Hoeber, Inc., 1932.

THE HEART RATE. By Ernst P. Boas, M.D., Associate Physician, Mount Sinai Hospital, New York, and Ernst F. Goldschmidt, Ph.D., Research Fellow (1930-31), Department of Surgery, Yale University School of Medicine. Price, $3.50. Pp. 166, with 68 figures. Springfield, Ill.: Charles C. Thomas, 1932.

REPORT OF THE LABORATORY AND MUSEUM OF COMPARATIVE PATHOLOGY OF THE ZOOLOGICAL SOCIETY OF PHILADELPHIA. By Herbert Fox, M.D., Pathologist, 1932.

THE SIGN OF BABINSKI: A STUDY OF THE EVOLUTION OF CORTICAL DOMINANCE IN PRIMATES. By John F. Fulton, Sterling Professor of Physiology in the Yale University School of Medicine, and Allen D. Keller, Professor of Physiology and Pharmacology in the School of Medicine, University of Alabama. Price, cloth, $5. Pp. 166, with 66 illustrations. Springfield, Ill.: Charles C. Thomas, 1932.